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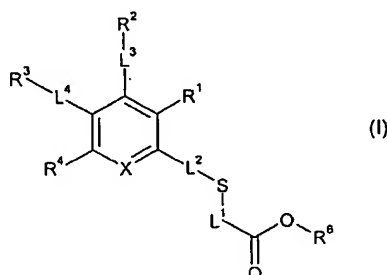
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(54) Title: GLYOXALASE INHIBITORS



(57) Abstract: This invention relates to compounds of formula (I) which are glyoxalase I inhibitors, pharmaceutical salts or compositions comprising such compounds, and the use of such compositions and compounds to treat various conditions alleviated by the inhibition of glyoxalase I. Wherein X is N or CH. R<sup>2</sup> is H, CF<sub>3</sub>; or optionally substituted C<sub>5-6</sub> aryl, C<sub>3-7</sub> cycloalkyl, C<sub>5-7</sub> heterocyclyl. R<sup>3</sup> is H; or optionally substituted C<sub>5-6</sub> aryl, C<sub>3-7</sub> cycloalkyl, C<sub>5-7</sub> heterocyclyl. Alternatively R<sup>2</sup> and R<sup>3</sup> together form an optionally substituted C<sub>3-4</sub>alkylene group wherein L<sup>3</sup> and L<sup>4</sup> are single bonds thus forming a C<sub>5-6</sub> ring fused with the aromatic ring to which L<sup>3</sup> and L<sup>4</sup> are attached. L<sup>3</sup> and L<sup>4</sup> are independently selected from a single bond, optionally substituted C<sub>1-4</sub> alkylene, -L<sup>9</sup>YN(OH)C(=O)L<sup>10</sup>- and -L<sup>9</sup>C(=O)N(OH)YL<sup>10</sup>-, wherein L<sup>9</sup> and L<sup>10</sup> are independently selected from optionally substituted C<sub>1-4</sub> alkylene, C<sub>5-6</sub> arylene, C<sub>1-4</sub> alkylene-C<sub>5-6</sub>arylene and a single bond, wherein Y is NH or a single bond.

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## GLYOXALASE INHIBITORS

This invention relates to compounds which are glyoxalase I inhibitors, pharmaceutical compositions comprising such compounds, and the use of such compositions and compounds to treat various conditions alleviated by the inhibition of glyoxalase I.

10 Background to the invention

Methyl glyoxal (MG) is an endogenous cytotoxic agent that is formed in cells as a consequence of glycolysis. The glyoxalase system converts 2-oxoaldehydes such as MG into the corresponding 2-hydroxy acid in two consecutive steps.

15 MG is converted to D-lactate via the intermediate S-D-lactoylglutathione. The glyoxalase system comprises two enzymes, glyoxalase I and glyoxalase II. Glyoxalase I is the rate limiting enzyme, and catalyses the formation of S-D-lactoylglutathione from the hemithioacetal formed non-enzymatically from MG and reduced glutathione (GSH).  
20 Glyoxalase II catalyses the hydrolysis of S-D-lactoylglutathione to D-lactate, reforming the GSH consumed in the glyoxalase I-catalysed reaction (Thornalley et al., *Crit. Rev. Oncol. Haematol.* 20, 99 (1995)).

25 High levels of MG form DNA adducts and are generally toxic to cells. Cells having high glycolytic rates such as tumour cells and certain parasites have increased levels of glyoxalase I, which is believed to be the major  
30 detoxification pathway for MG. Glyoxalase-I levels were shown to be higher in 38 human cancer cell lines than in normal cells (Sakamoto et al., *Clin. Cancer Res.* 7, 2513 (2001)). Elevated glyoxalase I levels were observed in the

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following human cancer types: lung (Sakamoto et al., *ibid.*), prostate (Sakamoto et al., *ibid.*; Davidson et al., *J. Urol.* **161**, 690 (1999); Samadi et al., *Urology* **57**, 183 (2001)), colon (Ranganathan et al., *Biochim. Biophys. Acta* **1182**, 311 (1993)), leukemia (Sakamoto et al., *Blood* **95**, 3214 (2000)) and breast (Rulli et al., *Breast Canc. Res. Treat* **66**, 67 (2001)). Agents that lead to an accumulation of MG, such as glyoxalase inhibitors, might be expected to exert an anti-tumor action (Thornalley et al., *Gen. Pharmacol.* **27**, 565 (1996)) and are therefore likely to have a beneficial effect on patients suffering from various forms of cancer.

Prototype peptidic glyoxalase I inhibitors have been synthesised, based on knowledge of the substrate of glyoxalase I, i.e. the hemithioacetal formed from MG and GSH (Johansson et al., *Mol. Pharmacol.* **57**, 619 (2000); Thornalley et al. *J. Med. Chem.* **39**, 3409 (1996); Kalsi et al., *J. Med. Chem.* **42**, 3981 (2000); Sharkey et al., *Cancer Chemother. Pharmacol.* **46**, 156 (2000)). Such inhibitors have been shown to acutely increase MG levels and induce apoptosis in cancer cells. Additionally they have been shown to exert anti-cancer effects *in vivo*, both on their own and synergising with existing cytotoxic agents (Thornalley et al., *Biochem. Pharmacol.* **51**, 1365 (1996); Sakamoto et al., *Blood* **95**, 3214 (2000); Sharkey et al., *ibid.*). Moreover, there is increasing evidence that tumour cell resistance to certain cytotoxics (adriamycin, etoposide) may result, in part, from the over-activity of glyoxalase I (Sakamoto et al., *Blood* **95**, 3214 (2000); Johansson et al., *ibid.*).

Known glyoxalase I inhibitor compounds are generally peptidic and require esterification to gain access to the

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interior of the cell where glyoxalase I is found. It is therefore desirable to find classes of glyoxalase I inhibitor compounds which are non-peptidic and hence have greater potential as therapeutic agents.

5

US Patent 4,898,870 describes pyrroloquinoline quinone compounds in relation to glyoxalase I inhibition, although no activity data for glyoxalase I inhibition is disclosed. WO 99/35128 is related to competitive inhibitor compounds of glyoxalase I, and a method of generating such inhibitors inside tumour cells using an acyl-interchange reaction between a membrane-permeable prodrug and intracellular glutathione.

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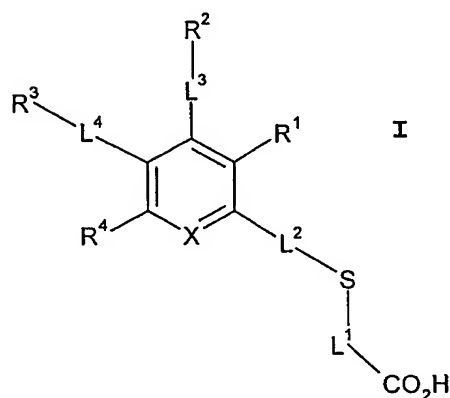
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The invention provides further classes of glyoxalase I inhibitor compounds which are non-peptidic, and therefore have greater potential as therapeutic agents.

#### Summary of the invention

20

A first aspect of the present invention provides a compound of formula I:



wherein

X is N or CH;

25

R<sup>1</sup> is H, cyano, halo, hydroxy, hydroxamic acid,

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sulfhydryl or  $-NH_2$ ; or  $C_{1-4}$  alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or  $-NH_2$ ; or  $-OR$ ,  $-NHR$ ,  $-NR_2$  or  $-SR$  wherein  $R$  is  $C_{1-4}$  alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or  $-NH_2$ ;

$R^2$  is  $H$ ,  $CF_3$ ; or optionally substituted  $C_{5-6}$  aryl,  $C_{3-7}$  cycloalkyl,  $C_{5-7}$  heterocyclyl or together with  $R^3$  an optionally substituted  $C_{3-4}$  alkylene group wherein  $L^3$  and  $L^4$  are single bonds thus forming a  $C_{5-6}$  ring fused with the aromatic ring to which  $L^3$  and  $L^4$  are attached;

$R^3$  is  $H$ ; or optionally substituted  $C_{5-6}$  aryl,  $C_{3-7}$  cycloalkyl,  $C_{5-7}$  heterocyclyl or together with  $R^2$  an optionally substituted  $C_{3-4}$  alkylene group wherein  $L^3$  and  $L^4$  are single bonds thus forming a  $C_{5-6}$  ring fused with the aromatic ring to which  $L^3$  and  $L^4$  are attached;

$R^4$  is  $H$ ; or optionally substituted  $C_{5-6}$  aryl or  $C_{5-7}$  heterocyclyl;

$L^1$  is optionally substituted  $C_{1-4}$  alkylene,  $C_{5-6}$  arylene,  $C_{1-4}$  alkylene- $C_{5-6}$  arylene or  $-L^5N(R^5)L^6-$ , wherein  $L^5$  and  $L^6$  are independently selected from optionally substituted  $C_{1-4}$  alkylene and  $C_{5-6}$  arylene, and  $R^5$  is  $H$  or  $C_{1-4}$  alkyl;

$L^2$  is a single bond; or optionally substituted  $C_{1-4}$  alkylene or  $-L^7C(=O)L^8-$ , wherein  $L^7$  and  $L^8$  are independently selected from optionally substituted  $C_{1-4}$  alkylene and a single bond; and

$L^3$  and  $L^4$  are independently selected from a single bond, optionally substituted  $C_{1-4}$  alkylene,  $-L^9YN(OH)C(=O)L^{10}-$  and  $-L^9C(=O)N(OH)YL^{10}-$ , wherein  $L^9$  and  $L^{10}$  are independently selected from optionally substituted  $C_{1-4}$  alkylene,  $C_{5-6}$  arylene,  $C_{1-4}$  alkylene- $C_{5-6}$  arylene and a single bond, wherein  $Y$  is  $NH$  or a single bond;

or a pharmaceutically acceptable salt thereof for use in a method of therapy.

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A second aspect of the present invention provides a pharmaceutical composition comprising a compound of formula I as defined in the first aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

A further aspect of the present invention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by inhibition of glyoxalase I.

Another aspect of the present invention provides a method of treating a condition which can be alleviated by inhibition of glyoxalase I, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides novel compounds or salts, solvates and chemically protected forms thereof, and methods of synthesis thereof as described herein.

In this aspect, the compounds are as provided in formula I wherein the compounds contain at least one  $-C(=O)N(OH)-$  group.

Conditions alleviated by inhibition of glyoxalase I are proliferative conditions. The term "proliferative condition" pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is

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undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*.

Examples of proliferative conditions include, but are not limited to, benign, pre-malignant, and malignant cellular proliferation, including but not limited to, neoplasms and tumours (e.g., histocytoma, glioma, astrocytoma, osteoma), cancers (e.g., lung cancer, small cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma), leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

#### Definitions

Cyano: The term "cyano", as used herein, pertains to the monovalent moiety -CN.

25

Halo: The term "halo", as used herein, pertains to the monovalent moiety -Y, wherein Y is a halogen atom. Examples of halo groups include -F, -Cl, -Br, and -I.

30 Hydroxy: The term "hydroxy", as used herein, pertains to the monovalent moiety -OH.

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Hydroxamic acid: The term "hydroxamic acid", as used herein, pertains to the monovalent moiety  $\text{-C(=O)NH(OH)}$ .

5 Sulfhydryl: The term "sulfhydryl", as used herein, pertains to the monovalent moiety  $\text{-SH}$ .

$\text{C}_{1-4}$  alkyl group: The term " $\text{C}_{1-4}$  alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a non-cyclic hydrocarbon  
10 compound having from 1 to 4 carbon atoms, and which may be saturated or unsaturated.

Examples of saturated  $\text{C}_{1-4}$  alkyl groups include methyl ( $\text{C}_1$ ); ethyl ( $\text{C}_2$ ); propyl ( $\text{C}_3$ ), which may be linear (n-propyl) or  
15 branched (iso-propyl); butyl ( $\text{C}_4$ ), which may be linear (n-butyl) or branched (iso-butyl, sec-butyl and tert-butyl).

Examples of unsaturated  $\text{C}_{1-4}$  alkyl groups, which may be referred to as  $\text{C}_{1-4}$  alkenyl (if they included a double bond)  
20 or  $\text{C}_{1-4}$  alkynyl (if they include a triple bond) groups, include ethenyl (vinyl,  $\text{-CH=CH}_2$ ), ethynyl (ethynyl,  $\text{-C}\equiv\text{CH}$ ), 1-propenyl ( $\text{-CH=CH-CH}_3$ ), 2-propenyl (allyl,  $\text{-CH-CH=CH}_2$ ), 2-propynyl (propargyl,  $\text{-CH}_2\text{-C}\equiv\text{CH}$ ), isopropenyl ( $\text{-C(CH}_3\text{)=CH}_2$ ) and butenyl ( $\text{C}_4$ ).

25  $\text{C}_{3-7}$  Cycloalkyl: The term " $\text{C}_{3-7}$  cycloalkyl", as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon  
30 (carbocyclic) compound, which moiety has from 3 to 7 ring atoms (unless otherwise specified).



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Examples of saturated cycloalkyl groups include, but are not limited to, those derived from: cyclopropane (C<sub>3</sub>), cyclobutane (C<sub>4</sub>), cyclopentane (C<sub>5</sub>), cyclohexane (C<sub>6</sub>), cycloheptane (C<sub>7</sub>), norbornane (C<sub>7</sub>), norpinane (C<sub>7</sub>), norcarane (C<sub>7</sub>).

C<sub>5-7</sub> Heterocyclyl: The term "C<sub>5-7</sub> heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 5 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefix C<sub>5-7</sub> denotes the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C<sub>5-7</sub> heterocyclyl" as used herein, pertains to a heterocyclyl group having 5 to 7 ring atoms. Examples of groups of heterocyclyl groups include C<sub>5-7</sub> heterocyclyl and C<sub>5-6</sub> heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N<sub>1</sub>: pyrrolidine (tetrahydropyrrole) (C<sub>5</sub>), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C<sub>5</sub>), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C<sub>5</sub>), piperidine (C<sub>6</sub>), dihydropyridine (C<sub>6</sub>), tetrahydropyridine (C<sub>6</sub>), azepine (C<sub>7</sub>);  
O<sub>1</sub>: oxolane (tetrahydrofuran) (C<sub>5</sub>), oxole (dihydrofuran) (C<sub>5</sub>), oxane (tetrahydropyran) (C<sub>6</sub>), dihydropyran (C<sub>6</sub>), pyran (C<sub>6</sub>), oxepin (C<sub>7</sub>);  
S<sub>1</sub>: thiolane (tetrahydrothiophene) (C<sub>5</sub>), thiane (tetrahydrothiopyran) (C<sub>6</sub>), thiopane (C<sub>7</sub>);  
O<sub>2</sub>: dioxolane (C<sub>5</sub>), dioxane (C<sub>6</sub>), and dioxepane (C<sub>7</sub>);

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O<sub>3</sub>: trioxane (C<sub>6</sub>);

N<sub>2</sub>: imidazolidine (C<sub>5</sub>), pyrazolidine (diazolidine) (C<sub>5</sub>),  
imidazoline (C<sub>5</sub>), pyrazoline (dihydropyrazole) (C<sub>5</sub>),  
piperazine (C<sub>6</sub>);

5 N<sub>1</sub>O<sub>1</sub>: tetrahydrooxazole (C<sub>5</sub>), dihydrooxazole (C<sub>5</sub>),  
tetrahydroisoxazole (C<sub>5</sub>), dihydroisoxazole (C<sub>5</sub>), morpholine  
(C<sub>6</sub>), tetrahydrooxazine (C<sub>6</sub>), dihydrooxazine (C<sub>6</sub>), oxazine  
(C<sub>6</sub>);

10 N<sub>1</sub>S<sub>1</sub>: thiazoline (C<sub>5</sub>), thiazolidine (C<sub>5</sub>),  
thiomorpholine (C<sub>6</sub>);

N<sub>2</sub>O<sub>1</sub>: oxadiazine (C<sub>6</sub>);

O<sub>1</sub>S<sub>1</sub>: oxathiole (C<sub>5</sub>) and oxathiane (thioxane) (C<sub>6</sub>); and,

N<sub>1</sub>O<sub>1</sub>S<sub>1</sub>: oxathiazine (C<sub>6</sub>).

15 Examples of substituted (non-aromatic) monocyclic  
heterocyclyl groups include those derived from saccharides,  
in cyclic form, for example, furanoses (C<sub>5</sub>), such as  
arabinofuranose, lyxofuranose, ribofuranose, and  
xylofuranse, and pyranoses (C<sub>6</sub>), such as allopyranose,  
20 altropyranose, glucopyranose, mannopyranose, gulopyranose,  
idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl  
groups are described below with aryl groups.

25

C<sub>5-6</sub> aryl: The term "C<sub>5-6</sub> aryl", as used herein, pertains to a  
monovalent moiety obtained by removing a hydrogen atom from  
an aromatic ring atom of an aromatic compound, which moiety  
has from 5 to 6 ring atoms (unless otherwise specified).

30 In this context, the prefix C<sub>5-6</sub> denotes the number of ring  
atoms, or range of number of ring atoms, whether carbon  
atoms or heteroatoms. For example, the term "C<sub>5-6</sub> aryl," as

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used herein, pertains to an aryl group having 5 or 6 ring atoms.

The ring atoms may be all carbon atoms, as in "carboaryl groups." Examples of carboaryl groups include C<sub>5-6</sub> carboaryl, C<sub>5</sub> carboaryl, and C<sub>6</sub> carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C<sub>6</sub>).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups." Examples of heteroaryl groups include C<sub>5-6</sub> heteroaryl, C<sub>5</sub> heteroaryl, and C<sub>6</sub> heteroaryl.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N<sub>1</sub>: pyrrole (azole) (C<sub>5</sub>), pyridine (azine) (C<sub>6</sub>);

O<sub>1</sub>: furan (oxole) (C<sub>5</sub>);

S<sub>1</sub>: thiophene (thiole) (C<sub>5</sub>);

N<sub>1</sub>O<sub>1</sub>: oxazole (C<sub>5</sub>), isoxazole (C<sub>5</sub>), isoxazine (C<sub>6</sub>);

N<sub>2</sub>O<sub>1</sub>: oxadiazole (furazan) (C<sub>5</sub>);

N<sub>3</sub>O<sub>1</sub>: oxatriazole (C<sub>5</sub>);

N<sub>1</sub>S<sub>1</sub>: thiazole (C<sub>5</sub>), isothiazole (C<sub>5</sub>);

N<sub>2</sub>: imidazole (1,3-diazole) (C<sub>5</sub>), pyrazole (1,2-diazole) (C<sub>5</sub>), pyridazine (1,2-diazine) (C<sub>6</sub>), pyrimidine (1,3-diazine) (C<sub>6</sub>) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C<sub>6</sub>);

N<sub>3</sub>: triazole (C<sub>5</sub>), triazine (C<sub>6</sub>); and,

N<sub>4</sub>: tetrazole (C<sub>5</sub>).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be

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N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methylpyrrole. Examples of N-substitutents include, but are not limited to C<sub>1-4</sub> alkyl, C<sub>5-7</sub> heterocyclyl, C<sub>5-6</sub> aryl, and acyl groups.

5

The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties.

10

C<sub>1-4</sub> alkylene: The term "C<sub>1-4</sub> alkylene" as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms from opposite ends of a linear hydrocarbon compound having from 1 to 4 carbon atoms (unless otherwise specified), and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkylene" includes the sub-classes alkenylene, alkynylene, etc., discussed below.

15

20 In this context, the prefix C<sub>1-4</sub> denotes the number of carbon atoms, or range of number of carbon atoms. For example, the term "C<sub>1-4</sub> alkylene" as used herein, pertains to an alkylene group having from 1 to 4 carbon atoms.

25

Examples of saturated C<sub>1-4</sub> alkylene groups include, but are not limited to, -(CH<sub>2</sub>)<sub>n</sub>- where n is an integer from 1 to 4, for example, -CH<sub>2</sub>- (methylene), -CH<sub>2</sub>CH<sub>2</sub>- (ethylene), -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- (propylene), and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- (butylene).

30

Examples of partially unsaturated C<sub>1-4</sub> alkylene groups include, but are not limited to, -CH=CH- (vinylene), -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH=CH-.

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C<sub>5-6</sub> arylene: The term "C<sub>5-6</sub> arylene", as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, one from each of two different aromatic ring atoms of an aromatic compound, which moiety has from 5 to 6  
5 ring atoms (unless otherwise specified).

In this context, the prefix C<sub>5-6</sub> denotes the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C<sub>5-6</sub> arylene"  
10 as used herein, pertains to an arylene group having 5 or 6 ring atoms. Examples of groups of arylene groups include C<sub>5-6</sub> arylene, C<sub>5</sub> arylene, and C<sub>6</sub> arylene.

The ring atoms may be all carbon atoms, as in "carboarylene  
15 groups" (e.g., C<sub>5-6</sub> carboarylene).

Examples of C<sub>5-6</sub> arylene groups which do not have ring heteroatoms (i.e., C<sub>5-6</sub> carboarylene groups) include, but are not limited to, those derived from the compounds discussed  
20 above in regard to carboaryl groups.

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroarylene groups" (e.g., C<sub>5-6</sub> heteroarylene).  
25

Examples of C<sub>5-6</sub> heteroarylene groups include, but are not limited to, those derived from the compounds discussed above in regard to heteroaryl groups.

C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene: The term "C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene", as used herein, pertains to a bidentate moiety comprising a C<sub>1-4</sub> alkylene moiety, -C<sub>1-4</sub> alkylene-, linked to  
30

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a C<sub>5-6</sub> arylene moiety, -C<sub>5-6</sub> arylene-, that is, -C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene-.

Examples of C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene groups include, for example, methylene-phenylene, ethylene-phenylene, propylene-phenylene, and ethenylene-phenylene (also known as vinylene-phenylene).

The phrase "optionally substituted", as used herein, pertains to a group, as above, which may be unsubstituted or which may be substituted by one of the following substituent groups or one of the groups listed above:

C<sub>1-7</sub> alkyl group: The term "C<sub>1-7</sub> alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the subclasses alkenyl, alkynyl and cycloalkyl discussed below.

In this context, the prefixes (e.g. C<sub>1-4</sub>, C<sub>1-7</sub>, C<sub>2-7</sub>, C<sub>3-7</sub>, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C<sub>1-4</sub> alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C<sub>1-4</sub> alkyl ("lower alkyl") and C<sub>1-7</sub> alkyl.

Examples of saturated alkyl groups include, but are not limited to, methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), propyl (C<sub>3</sub>), butyl (C<sub>4</sub>), pentyl (C<sub>5</sub>), hexyl (C<sub>6</sub>), heptyl (C<sub>7</sub>).

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Examples of saturated linear alkyl groups include, but are not limited to, methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), n-propyl (C<sub>3</sub>), n-butyl (C<sub>4</sub>), n-pentyl (amyl) (C<sub>5</sub>), n-hexyl (C<sub>6</sub>), and n-heptyl (C<sub>7</sub>).

5

Examples of saturated branched alkyl groups include iso-propyl (C<sub>3</sub>), iso-butyl (C<sub>4</sub>), sec-butyl (C<sub>4</sub>), tert-butyl (C<sub>4</sub>), iso-pentyl (C<sub>5</sub>), and neo-pentyl (C<sub>5</sub>).

10 Cycloalkyl: The term "cycloalkyl", as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless  
15 otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

Examples of saturated cycloalkyl groups include, but are not limited to, those derived from: cyclopropane (C<sub>3</sub>),  
20 cyclobutane (C<sub>4</sub>), cyclopentane (C<sub>5</sub>), cyclohexane (C<sub>6</sub>), cycloheptane (C<sub>7</sub>), norbornane (C<sub>7</sub>), norpinane (C<sub>7</sub>), norcarane (C<sub>7</sub>), adamantane (C<sub>10</sub>), and decalin (decahydronaphthalene) (C<sub>10</sub>).

25 Examples of saturated cycloalkyl groups, which are also referred to herein as "alkyl-cycloalkyl" groups, include, but are not limited to, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl,  
30 and dimethylcyclohexyl, menthane, thujane, carane, pinane, bornane, norcarane, and camphene.

- 15 -

Examples of unsaturated cyclic alkenyl groups, which are also referred to herein as "alkyl-cycloalkenyl" groups, include, but are not limited to, methylcyclopropenyl, dimethylcyclopropenyl, methylcyclobutenyl, dimethylcyclobutenyl, methylcyclopentenyl, dimethylcyclopentenyl, methylcyclohexenyl, and dimethylcyclohexenyl.

Examples of cycloalkyl groups, with one or more other rings fused to the parent cycloalkyl group, include, but are not limited to, those derived from: indene (C<sub>9</sub>), indan (e.g., 2,3-dihydro-1H-indene) (C<sub>9</sub>), tetraline (1,2,3,4-tetrahydronaphthalene (C<sub>10</sub>), acenaphthene (C<sub>12</sub>), fluorene (C<sub>13</sub>), phenalene (C<sub>13</sub>), acephenanthrene (C<sub>15</sub>), aceanthrene (C<sub>16</sub>). For example, 2H-inden-2-yl is a C<sub>5</sub>cycloalkyl group with a substituent (phenyl) fused thereto.

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds.

Examples of groups of alkenyl groups include C<sub>2-4</sub> alkenyl, C<sub>2-7</sub> alkenyl, C<sub>2-20</sub> alkenyl.

Examples of unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH<sub>2</sub>), 1-propenyl (-CH=CH-CH<sub>3</sub>), 2-propenyl (allyl, -CH-CH=CH<sub>2</sub>), isopropenyl (-C(CH<sub>3</sub>)=CH<sub>2</sub>), butenyl (C<sub>4</sub>), pentenyl (C<sub>5</sub>), and hexenyl (C<sub>6</sub>).

Examples of unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C<sub>3</sub>), cyclobutenyl (C<sub>4</sub>), cyclopentenyl (C<sub>5</sub>), and cyclohexenyl (C<sub>6</sub>).



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Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C<sub>2-4</sub> alkynyl, C<sub>2-7</sub> alkynyl, C<sub>2-20</sub> alkynyl.

5

Examples of unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH<sub>2</sub>-C≡CH).

10 C<sub>3-7</sub> heterocyclyl group: The term "C<sub>3-7</sub> heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 7 ring atoms (unless otherwise specified), of which from 1 to 4 are ring heteroatoms.

15

In this context, the prefixes (e.g. C<sub>3-7</sub>, C<sub>5-6</sub> etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C<sub>5-6</sub> heterocyclyl", as used herein, pertains to a

20 heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C<sub>3-7</sub> heterocyclyl, C<sub>5-7</sub> heterocyclyl.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

25

N<sub>1</sub>: aziridine (C<sub>3</sub>), azetidine (C<sub>4</sub>), pyrrolidine

(tetrahydropyrrole) (C<sub>5</sub>), pyrroline (e.g., 3-pyrroline,

2,5-dihydropyrrole) (C<sub>5</sub>), 2H-pyrrole or 3H-pyrrole

(isopyrrole, isoazole) (C<sub>5</sub>), piperidine (C<sub>6</sub>),

30 dihydropyridine (C<sub>6</sub>), tetrahydropyridine (C<sub>6</sub>), azepine (C<sub>7</sub>);

O<sub>1</sub>: oxirane (C<sub>3</sub>), oxetane (C<sub>4</sub>), oxolane (tetrahydrofuran)

(C<sub>5</sub>), oxole (dihydrofuran) (C<sub>5</sub>), oxane (tetrahydropyran)

(C<sub>6</sub>), dihydropyran (C<sub>6</sub>), pyran (C<sub>6</sub>), oxepin (C<sub>7</sub>);

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S<sub>1</sub>: thiirane (C<sub>3</sub>), thietane (C<sub>4</sub>), thiolane (tetrahydrothiophene) (C<sub>5</sub>), thiane (tetrahydrothiopyran) (C<sub>6</sub>), thiepane (C<sub>7</sub>);

O<sub>2</sub>: dioxolane (C<sub>5</sub>), dioxane (C<sub>6</sub>), and dioxepane (C<sub>7</sub>);

5 O<sub>3</sub>: trioxane (C<sub>6</sub>);

N<sub>2</sub>: imidazolidine (C<sub>5</sub>), pyrazolidine (diazolidine) (C<sub>5</sub>), imidazoline (C<sub>5</sub>), pyrazoline (dihydropyrazole) (C<sub>5</sub>), piperazine (C<sub>6</sub>);

10 N<sub>1</sub>O<sub>1</sub>: tetrahydrooxazole (C<sub>5</sub>), dihydrooxazole (C<sub>5</sub>), tetrahydroisoxazole (C<sub>5</sub>), dihydroisoxazole (C<sub>5</sub>), morpholine (C<sub>6</sub>), tetrahydrooxazine (C<sub>6</sub>), dihydrooxazine (C<sub>6</sub>), oxazine (C<sub>6</sub>);

N<sub>1</sub>S<sub>1</sub>: thiazoline (C<sub>5</sub>), thiazolidine (C<sub>5</sub>), thiomorpholine (C<sub>6</sub>);

15 N<sub>2</sub>O<sub>1</sub>: oxadiazine (C<sub>6</sub>);

O<sub>1</sub>S<sub>1</sub>: oxathiole (C<sub>5</sub>) and oxathiane (thioxane) (C<sub>6</sub>); and,

N<sub>1</sub>O<sub>1</sub>S<sub>1</sub>: oxathiazine (C<sub>6</sub>).

20 C<sub>5-7</sub> aryl: The term "C<sub>5-7</sub> aryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 7 ring atoms (unless otherwise specified).

25 In this context, the prefixes (e.g. C<sub>5-7</sub>, C<sub>5-6</sub> etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C<sub>5-6</sub> aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C<sub>5-7</sub> aryl, C<sub>5-6</sub> aryl, C<sub>5</sub> aryl and C<sub>6</sub> aryl.

30

The ring atoms may be all carbon atoms, as in "carboaryl groups". Examples of carboaryl groups include C<sub>5-7</sub> carboaryl, C<sub>5-6</sub> carboaryl, C<sub>5</sub> carboaryl and C<sub>6</sub> carboaryl.

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Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C<sub>6</sub>).

- 5 Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups." Examples of heteroaryl groups include C<sub>5-7</sub> heteroaryl, C<sub>5-6</sub> heteroaryl, C<sub>5</sub> heteroaryl and C<sub>6</sub> heteroaryl.
- 10 Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:
- N<sub>1</sub>: pyrrole (azole) (C<sub>5</sub>), pyridine (azine) (C<sub>6</sub>);  
O<sub>1</sub>: furan (oxole) (C<sub>5</sub>);  
S<sub>1</sub>: thiophene (thiole) (C<sub>5</sub>);
- 15 N<sub>1</sub>O<sub>1</sub>: oxazole (C<sub>5</sub>), isoxazole (C<sub>5</sub>), isoxazine (C<sub>6</sub>);  
N<sub>2</sub>O<sub>1</sub>: oxadiazole (furazan) (C<sub>5</sub>);  
N<sub>3</sub>O<sub>1</sub>: oxatriazole (C<sub>5</sub>);  
N<sub>1</sub>S<sub>1</sub>: thiazole (C<sub>5</sub>), isothiazole (C<sub>5</sub>);  
N<sub>2</sub>: imidazole (1,3-diazole) (C<sub>5</sub>), pyrazole
- 20 (1,2-diazole) (C<sub>5</sub>), pyridazine (1,2-diazine) (C<sub>6</sub>),  
pyrimidine (1,3-diazine) (C<sub>6</sub>) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C<sub>6</sub>);  
N<sub>3</sub>: triazole (C<sub>5</sub>), triazine (C<sub>6</sub>); and,  
N<sub>4</sub>: tetrazole (C<sub>5</sub>).
- 25 Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methylpyrrole. Examples
- 30 of N-substitutents include, but are not limited to C<sub>1-7</sub> alkyl, C<sub>3-7</sub> heterocyclyl, C<sub>5-7</sub> aryl, and acyl groups.

Halo: -F, -Cl, -Br, and -I.

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Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C<sub>1-7</sub> alkyl group (also referred to as a C<sub>1-7</sub> alkoxy group, discussed below), a C<sub>3-7</sub> heterocyclyl group (also referred to as a C<sub>3-7</sub> heterocyclyloxy group), or a C<sub>5-7</sub> aryl group (also referred to as a C<sub>5-7</sub> aryloxy group), preferably a C<sub>1-7</sub> alkyl group.

C<sub>1-7</sub> alkoxy: -OR, wherein R is a C<sub>1-7</sub> alkyl group. Examples of C<sub>1-7</sub> alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C<sub>1-7</sub> alkyl group, a C<sub>3-7</sub> heterocyclyl group, or a C<sub>5-7</sub> aryl group, preferably hydrogen or a C<sub>1-7</sub> alkyl group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C<sub>1-7</sub> alkyl group (also referred to as C<sub>1-7</sub> alkylacyl or C<sub>1-7</sub> alkanoyl), a C<sub>3-7</sub> heterocyclyl group (also referred to as C<sub>3-7</sub> heterocyclylacyl), or a C<sub>5-7</sub> aryl group (also referred to as C<sub>5-7</sub> arylacyl), preferably a C<sub>1-7</sub> alkyl

- 20 -

group. Examples of acyl groups include, but are not limited to,  $-C(=O)CH_3$  (acetyl),  $-C(=O)CH_2CH_3$  (propionyl),  $-C(=O)C(CH_3)_3$  (t-butyryl), and  $-C(=O)Ph$  (benzoyl, phenone).

5 Carboxy (carboxylic acid):  $-C(=O)OH$ .

Thiocarboxy (thiocarboxylic acid):  $-C(=S)SH$ .

Thiolocarboxy (thiolocarboxylic acid):  $-C(=O)SH$ .

10

Thionocarboxy (thionocarboxylic acid):  $-C(=S)OH$ .

Imidic acid:  $-C(=NH)OH$ .

15 Hydroxamic acid:  $-C(=O)NH(OH)$ .

Ester (carboxylate, carboxylic acid ester, oxycarbonyl):

$-C(=O)OR$ , wherein R is an ester substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of ester groups include, but are not limited to,  $-C(=O)OCH_3$ ,  $-C(=O)OCH_2CH_3$ ,  $-C(=O)OC(CH_3)_3$ , and  $-C(=O)OPh$ .

20

Acyloxy (reverse ester):  $-OC(=O)R$ , wherein R is an acyloxy substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of acyloxy groups include, but are not limited to,  $-OC(=O)CH_3$  (acetoxy),  $-OC(=O)CH_2CH_3$ ,  $-OC(=O)C(CH_3)_3$ ,  $-OC(=O)Ph$ , and  $-OC(=O)CH_2Ph$ .

30

Oxycarboxyloxy:  $-OC(=O)OR$ , wherein R is an ester substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of

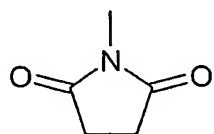
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ester groups include, but are not limited to,  $-\text{OC}(=\text{O})\text{OCH}_3$ ,  $-\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$ ,  $-\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$ , and  $-\text{OC}(=\text{O})\text{OPh}$ .

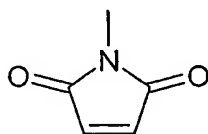
Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide):

- 5  $-\text{C}(=\text{O})\text{NR}^1\text{R}^2$ , wherein  $\text{R}^1$  and  $\text{R}^2$  are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to,  $-\text{C}(=\text{O})\text{NH}_2$ ,  $-\text{C}(=\text{O})\text{NHCH}_3$ ,  $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$ ,  $-\text{C}(=\text{O})\text{NHCH}_2\text{CH}_3$ , and  $-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$ , as well as amido groups in which  $\text{R}^1$  and  $\text{R}^2$ ,  
10 together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

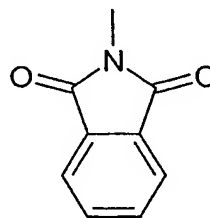
- 15 Acylamido (acylamino):  $-\text{NR}^1\text{C}(=\text{O})\text{R}^2$ , wherein  $\text{R}^1$  is an amide substituent, for example, hydrogen, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-7}$  heterocyclyl group, or a  $\text{C}_{5-7}$  aryl group, preferably hydrogen or a  $\text{C}_{1-7}$  alkyl group, and  $\text{R}^2$  is an acyl substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-7}$  heterocyclyl group, or a  
20  $\text{C}_{5-7}$  aryl group, preferably hydrogen or a  $\text{C}_{1-7}$  alkyl group. Examples of acylamide groups include, but are not limited to,  $-\text{NHC}(=\text{O})\text{CH}_3$ ,  $-\text{NHC}(=\text{O})\text{CH}_2\text{CH}_3$ , and  $-\text{NHC}(=\text{O})\text{Ph}$ .  $\text{R}^1$  and  $\text{R}^2$  may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



succinimidyl



maleimidyl



phthalimidyl

25 Thioamido (thiocarbamyl):  $-\text{C}(=\text{S})\text{NR}^1\text{R}^2$ , wherein  $\text{R}^1$  and  $\text{R}^2$  are independently amino substituents, as defined for amino

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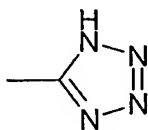
groups. Examples of amido groups include, but are not limited to,  $-C(=S)NH_2$ ,  $-C(=S)NHCH_3$ ,  $-C(=S)N(CH_3)_2$ , and  $-C(=S)NHCH_2CH_3$ .

- 5 Ureido:  $-N(R^1)CONR^2R^3$  wherein  $R^2$  and  $R^3$  are independently amino substituents, as defined for amino groups, and  $R^1$  is a ureido substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group. Examples of
- 10 ureido groups include, but are not limited to,  $-NHCONH_2$ ,  $-NHCONHMe$ ,  $-NHCONHEt$ ,  $-NHCONMe_2$ ,  $-NHCONEt_2$ ,  $-NMeCONH_2$ ,  $-NMeCONHMe$ ,  $-NMeCONHEt$ ,  $-NMeCONMe_2$ , and  $-NMeCONEt_2$ .

Guanidino:  $-NH-C(=NH)NH_2$ .

15

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



- 20 Amino:  $-NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently amino substituents, for example, hydrogen, a  $C_{1-7}$  alkyl group (also referred to as  $C_{1-7}$  alkylamino or di- $C_{1-7}$  alkylamino), a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably H or a  $C_{1-7}$  alkyl group, or, in the case of a "cyclic" amino group,
- 25  $R^1$  and  $R^2$ , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ( $-NH_2$ ), secondary ( $-NHR^1$ ), or tertiary ( $-NHR^1R^2$ ), and in cationic form, may be quaternary ( $-^+NR^1R^2R^3$ ). Examples of amino groups include,
- 30 but are not limited to,  $-NH_2$ ,  $-NHCH_3$ ,  $-NHC(CH_3)_2$ ,  $-N(CH_3)_2$ ,  $-N(CH_2CH_3)_2$ , and  $-NHPh$ . Examples of cyclic amino groups

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include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

- 5 Amidine (amidino):  $-C(=NR)NR_2$ , wherein each R is an amidine substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably H or a  $C_{1-7}$  alkyl group. Examples of amidine groups include, but are not limited to,  $-C(=NH)NH_2$ ,  $-C(=NH)NMe_2$ , and
- 10  $-C(=NMe)NMe_2$ .

Nitro:  $-NO_2$ .

Nitroso:  $-NO$ .

- 15 Cyano (nitrile, carbonitrile):  $-CN$ .

Isocyano:  $-NC$ .

- 20 Thiocyano (thiocyanato):  $-SCN$ .

Sulfhydryl (thiol, mercapto):  $-SH$ .

- Thioether (sulfide):  $-SR$ , wherein R is a thioether substituent, for example, a  $C_{1-7}$  alkyl group (also referred to as a  $C_{1-7}$  alkylthio group), a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of  $C_{1-7}$  alkylthio groups include, but are not limited to,  $-SCH_3$  and  $-SCH_2CH_3$ .
- 25

- 30 Disulfide:  $-SS-R$ , wherein R is a disulfide substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group (also referred



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to herein as C<sub>1-7</sub> alkyl disulfide). Examples of C<sub>1-7</sub> alkyl disulfide groups include, but are not limited to, -SSCH<sub>3</sub> and -SSCH<sub>2</sub>CH<sub>3</sub>.

- 5 Sulfine (sulfinyl, sulfoxide): -S(=O)R, wherein R is a sulfine substituent, for example, a C<sub>1-7</sub> alkyl group, a C<sub>3-7</sub> heterocyclyl group, or a C<sub>5-7</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples of sulfine groups include, but are not limited to, -S(=O)CH<sub>3</sub> and -S(=O)CH<sub>2</sub>CH<sub>3</sub>.

10

- Sulfone (sulfonyl): -S(=O)<sub>2</sub>R, wherein R is a sulfone substituent, for example, a C<sub>1-7</sub> alkyl group, a C<sub>3-7</sub> heterocyclyl group, or a C<sub>5-7</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group, including, for example, a fluorinated or  
15 perfluorinated C<sub>1-7</sub> alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)<sub>2</sub>CH<sub>3</sub> (methanesulfonyl, mesyl), -S(=O)<sub>2</sub>CF<sub>3</sub> (triflyl), -S(=O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (esyl), -S(=O)<sub>2</sub>C<sub>4</sub>F<sub>9</sub> (nonafllyl), -S(=O)<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> (tresyl), -S(=O)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> (tauryl), -S(=O)<sub>2</sub>Ph (phenylsulfonyl, besyl),  
20 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

- 25 Sulfinic acid (sulfino): -S(=O)OH, -SO<sub>2</sub>H.

Sulfonic acid (sulfo): -S(=O)<sub>2</sub>OH, -SO<sub>3</sub>H.

- Sulfinate (sulfinic acid ester): -S(=O)OR; wherein R is a  
30 sulfinate substituent, for example, a C<sub>1-7</sub> alkyl group, a C<sub>3-7</sub> heterocyclyl group, or a C<sub>5-7</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples of sulfinate groups include, but are not limited to, -S(=O)OCH<sub>3</sub> (methoxysulfinyl; methyl

- 25 -

sulfinate) and  $-S(=O)OCH_2CH_3$  (ethoxysulfinyl; ethyl sulfinate).

5 Sulfonate (sulfonic acid ester):  $-S(=O)_2OR$ , wherein R is a sulfonate substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of sulfonate groups include, but are not limited to,  $-S(=O)_2OCH_3$  (methoxysulfonyl; methyl sulfonate) and  $-S(=O)_2OCH_2CH_3$  (ethoxysulfonyl; ethyl  
10 sulfonate).

Sulfinyloxy:  $-OS(=O)R$ , wherein R is a sulfinyloxy substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$   
15 alkyl group. Examples of sulfinyloxy groups include, but are not limited to,  $-OS(=O)CH_3$  and  $-OS(=O)CH_2CH_3$ .

Sulfonyloxy:  $-OS(=O)_2R$ , wherein R is a sulfonyloxy substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$   
20 heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of sulfonyloxy groups include, but are not limited to,  $-OS(=O)_2CH_3$  (mesylate) and  $-OS(=O)_2CH_2CH_3$  (esylate).

25 Sulfate:  $-OS(=O)_2OR$ ; wherein R is a sulfate substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$  heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of sulfate groups include, but are not limited to,  $-OS(=O)_2OCH_3$  and  $-SO(=O)_2OCH_2CH_3$ .

30

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide):  $-S(=O)NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently amino substituents, as defined for amino groups. Examples of

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sulfamyl groups include, but are not limited to,  $-S(=O)NH_2$ ,  $-S(=O)NH(CH_3)$ ,  $-S(=O)N(CH_3)_2$ ,  $-S(=O)NH(CH_2CH_3)$ ,  $-S(=O)N(CH_2CH_3)_2$ , and  $-S(=O)NHPh$ .

- 5 Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide):  $-S(=O)_2NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to,  $-S(=O)_2NH_2$ ,  $-S(=O)_2NH(CH_3)$ ,  $-S(=O)_2N(CH_3)_2$ ,  $-S(=O)_2NH(CH_2CH_3)$ ,  
10  $-S(=O)_2N(CH_2CH_3)_2$ , and  $-S(=O)_2NHPh$ .

- Sulfamino:  $-NR^1S(=O)_2OH$ , wherein  $R^1$  is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to,  $-NHS(=O)_2OH$  and  
15  $-N(CH_3)S(=O)_2OH$ .

- Sulfonamino:  $-NR^1S(=O)_2R$ , wherein  $R^1$  is an amino substituent, as defined for amino groups, and  $R$  is a sulfonamino substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$   
20 heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of sulfonamino groups include, but are not limited to,  $-NHS(=O)_2CH_3$  and  $-N(CH_3)S(=O)_2C_6H_5$ .

- Sulfinamino:  $-NR^1S(=O)R$ , wherein  $R^1$  is an amino substituent, as defined for amino groups, and  $R$  is a sulfinamino substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-7}$   
25 heterocyclyl group, or a  $C_{5-7}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of sulfinamino groups include, but are not limited to,  $-NHS(=O)CH_3$  and  $-N(CH_3)S(=O)C_6H_5$ .

30

*Includes Other Forms*

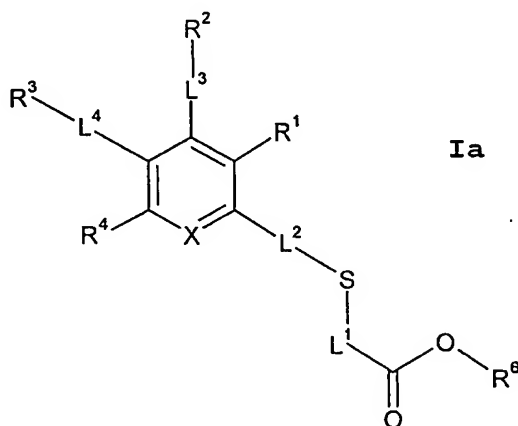
Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of

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these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form (-COO<sup>-</sup>), a salt or solvate thereof, as well as conventional protected forms such as esters. Similarly, a reference to an amino group includes the protonated form (-N<sup>+</sup>HR<sup>1</sup>R<sup>2</sup>), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form (-O<sup>-</sup>), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

#### *Ester derivatives*

The carboxylic acid moiety of compounds of formula I may be protected as an ester for example, as an optionally substituted C<sub>1-7</sub> alkyl ester (e.g. a methyl ester; a t-butyl ester; a chloroethyl ester); an optionally substituted C<sub>5-6</sub> aryl ester (e.g. a phenyl ester; a chlorophenyl ester; a tolyl ester); or an optionally substituted C<sub>1-4</sub> alkylene-C<sub>5-6</sub> aryl ester (e.g., a benzyl ester; a nitrobenzyl ester). Thus included in the above are compounds of formula Ia:



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wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $L^1$ ,  $L^2$ ,  $L^3$  and  $L^4$  are as defined above and  $R^6$  is selected from optionally substituted  $C_{1-7}$  alkyl,  $C_{5-6}$  aryl and  $C_{1-4}$  alkylene- $C_{5-6}$  aryl.

- 5  $C_{1-4}$  alkylene- $C_{5-6}$  aryl: The term " $C_{1-4}$  alkylene- $C_{5-6}$  aryl", as used herein, pertains to a bidentate moiety comprising a  $C_{1-4}$  alkylene moiety, - $C_{1-4}$  alkylene-, linked to a  $C_{5-6}$  aryl moiety, - $C_{5-6}$  aryl, that is, - $C_{1-4}$  alkylene- $C_{5-6}$  aryl.
- 10 Examples of  $C_{1-4}$  alkylene- $C_{5-6}$  aryl groups include, for example, methylene-phenyl (also known as benzyl), ethylene-phenyl, propylene-phenyl, and ethenylene-phenyl (also known as vinylene-phenylene).
- 15 The ester derivatives of formula Ia may function as prodrugs for the treatment of conditions alleviated by inhibition of glyoxalase I, i.e. proliferative conditions.

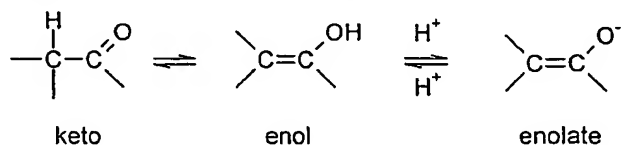
*Isomers, Salts, Solvates and Protected Forms*

- 20 Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms;
- 25 R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms;  $\alpha$ - and  $\beta$ -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof,
- 30 hereinafter collectively referred to as "isomers" (or "isomeric forms").

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Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group,  $-\text{OCH}_3$ , is not to be construed as a reference to its structural isomer, a hydroxymethyl group,  $-\text{CH}_2\text{OH}$ . Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g.,  $\text{C}_{1-7}$  alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidrine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including  $^1\text{H}$ ,  $^2\text{H}$  (D), and  $^3\text{H}$  (T); C may be in any isotopic form, including  $^{12}\text{C}$ ,  $^{13}\text{C}$ , and  $^{14}\text{C}$ ; O may be in any isotopic form, including  $^{16}\text{O}$  and  $^{18}\text{O}$ ; and the like.

- 30 -

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and  
5 separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

10 Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or  
15 handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

20

For example, if the compound is anionic, or has a functional group which may be anionic (e.g.,  $\text{-COOH}$  may be  $\text{-COO}^-$ ), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to,  
25 alkali metal ions such as  $\text{Na}^+$  and  $\text{K}^+$ , alkaline earth cations such as  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ , and other cations such as  $\text{Al}^{+3}$ .

Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e.,  $\text{NH}_4^+$ ) and substituted ammonium ions (e.g.,  $\text{NH}_3\text{R}^+$ ,  $\text{NH}_2\text{R}_2^+$ ,  $\text{NHR}_3^+$ ,  $\text{NR}_4^+$ ). Examples of  
30 some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine,

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choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is  $N(CH_3)_4^+$ .

- 5 If the compound is cationic, or has a functional group which may be cationic (e.g.,  $-NH_2$  may be  $-NH_3^+$ ), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric,  
10 hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

- Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids:  
15 2-acetoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic,  
20 methanesulfonic, mucic, oleic, oxalic, palmitic, pantoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to,  
25 those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

- It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The  
30 term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the



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solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or  
5 handle the active compound in a chemically protected form.

The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified

10 conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified

conditions. In a chemically protected form, one or more  
15 reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without

20 affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

25 A wide variety of such "protecting", "blocking", or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which  
30 would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a

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reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

5

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or  
10 t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH<sub>3</sub>, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH(OR)<sub>2</sub>) or ketal (R<sub>2</sub>C(OR)<sub>2</sub>), respectively, in  
15 which the carbonyl group (>C=O) is converted to a diether (>C(OR)<sub>2</sub>), by reaction with, for example, a primary alcohol.

The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

20

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH<sub>3</sub>); a benzyloxy amide (-NHCO-OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH<sub>3</sub>)<sub>3</sub>,  
25 -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>4</sub>C<sub>6</sub>H<sub>5</sub>, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide  
30 (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O·).

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For example, a carboxylic acid group may be protected as an ester for example, as: an C<sub>1-7</sub> alkyl ester (e.g., a methyl ester; a t-butyl ester); a C<sub>1-7</sub> haloalkyl ester (e.g., a C<sub>1-7</sub> trihaloalkyl ester); a triC<sub>1-7</sub> alkylsilyl-C<sub>1-7</sub> alkyl ester; 5 or a C<sub>5-7</sub> aryl-C<sub>1-7</sub> alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether 10 (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH<sub>2</sub>NHC(=O)CH<sub>3</sub>).

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and 15 therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, 20 amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included.

The term "therapeutically-effective amount," as used herein, 25 pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a 30 desired treatment regimen. Suitable dose ranges will typically be in the range of from 0.01 to 20 mg/kg/day, preferably from 0.1 to 10 mg/kg/day.

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*Compositions and their administration*

Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, acetylated triglycerides and the like, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also

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contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

Dosage forms or compositions containing active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier may be prepared.

For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, sodium crosscarmellose, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium, carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 1%-95% active ingredient, more preferably 2-50%, most preferably 5-8%.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional

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forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, triethanolamine sodium acetate, etc.

The percentage of active compound contained in such parental compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.1% to 10% in solution are employable, and will be higher if the composition is a solid which will be subsequently diluted to the above percentages. Preferably, the composition will comprise 0.2-2% of the active agent in solution.

#### *Acronyms*

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH),

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methylethyl ketone (MEK), ether or diethyl ether (Et<sub>2</sub>O),  
acetic acid (AcOH), dichloromethane (methylene chloride,  
DCM), acetonitrile (ACN), trifluoroacetic acid (TFA),  
dimethylformamide (DMF), tetrahydrofuran (THF), and  
5 dimethylsulfoxide (DMSO).

### General Synthesis Methods

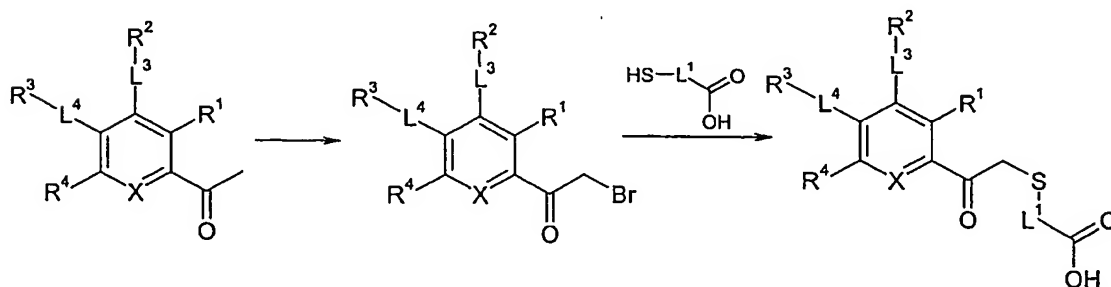
Methods for the chemical synthesis of compounds of the  
present invention are described herein. These methods may be  
10 modified and/or adapted in known ways in order to facilitate  
the synthesis of additional compounds within the scope of  
the present invention. Descriptions of general laboratory  
methods and procedures, useful for the preparation of the  
compounds of the present invention, are described in Vogel's  
15 Textbook of Practical Organic Chemistry (5<sup>th</sup> edition, Ed.  
Furniss, B.S., Hannaford, A.J., Smith, P.W.G., Tatchell,  
A.R., Longmann, UK).

In the methods described below, other substituent groups to  
20 those introduced may be present as precursors of those  
groups, or as protected versions of those groups.

Compounds of formula I where L<sup>2</sup> is -C(=O)-CH<sub>2</sub>-, can be  
synthesised according to the route shown in Scheme 1.

25

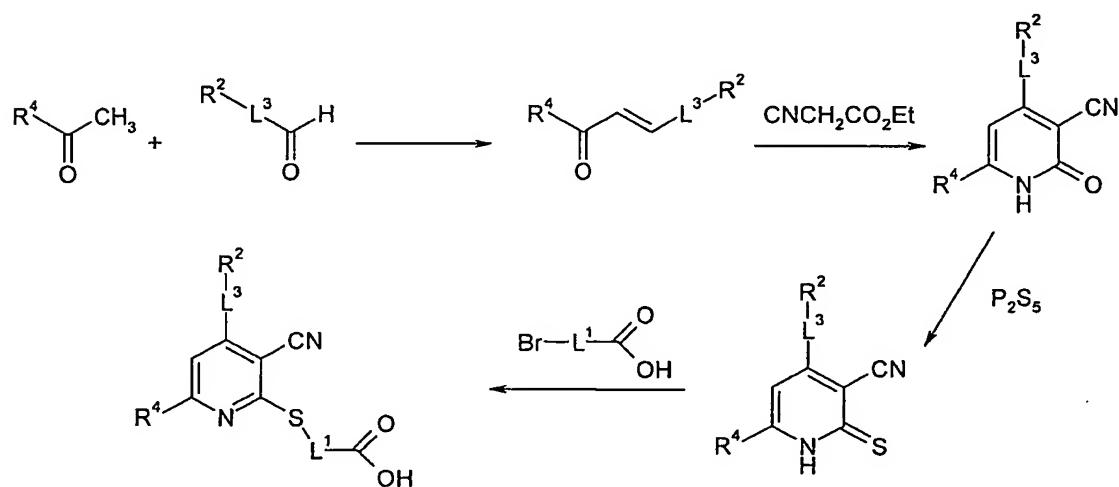
Scheme 1



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Compounds of formula I where X is N, L<sub>2</sub> is a single bond, R<sub>1</sub> = CN and R<sub>3</sub> = H can be synthesised according to the route based on those disclosed in Manna *et al.*, *Bioorg. Med. Chem. Lett.* **10**, 1883-1885 (2000) and Salman, *Pharmazie* **54**, 178-183 (1999) (scheme 2).

Scheme 2



(X=N, L<sup>2</sup>=single bond, R<sup>1</sup>=CN, R<sup>3</sup>=H)

10

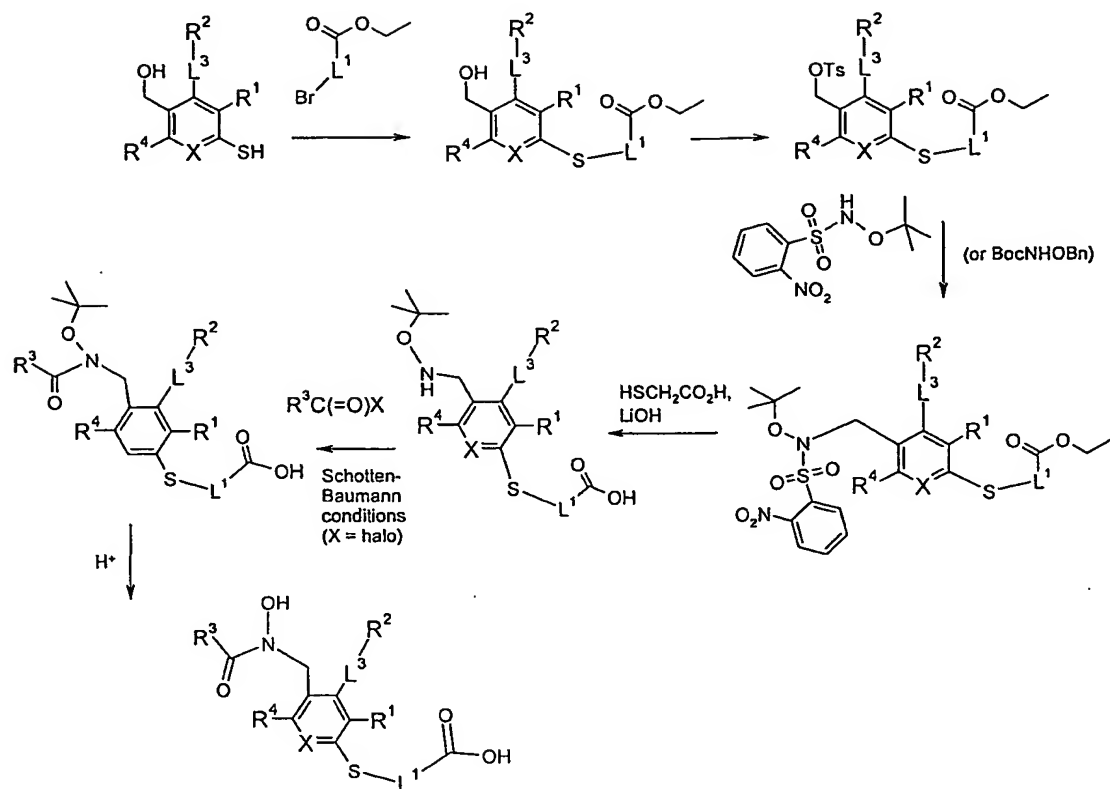
Compounds of formula I where L<sub>2</sub> is a single bond and L<sub>4</sub> = -CH<sub>2</sub>N(OH)C(=O)- can be synthesised according to the route based on that shown in Scheme 3. Compounds of formula I where L<sub>2</sub> is a single bond and L<sub>3</sub> = -CH<sub>2</sub>N(OH)C(=O)- can also be synthesised by a route based on that shown in Scheme 3, except that the starting material comprises a hydroxymethyl group present in the *meta* position relative to the thiol group, rather than in the *para* position as shown in scheme 3.

20



- 40 -

Scheme 3



As shown in the above three schemes, the sulfur atom between  
 5  $\text{L}^2$  and  $\text{L}^1$  may be introduced as a nucleophilic attacking  
 group (scheme 1) or by replacement (scheme 2), or may be  
 present in the starting material (scheme 3).

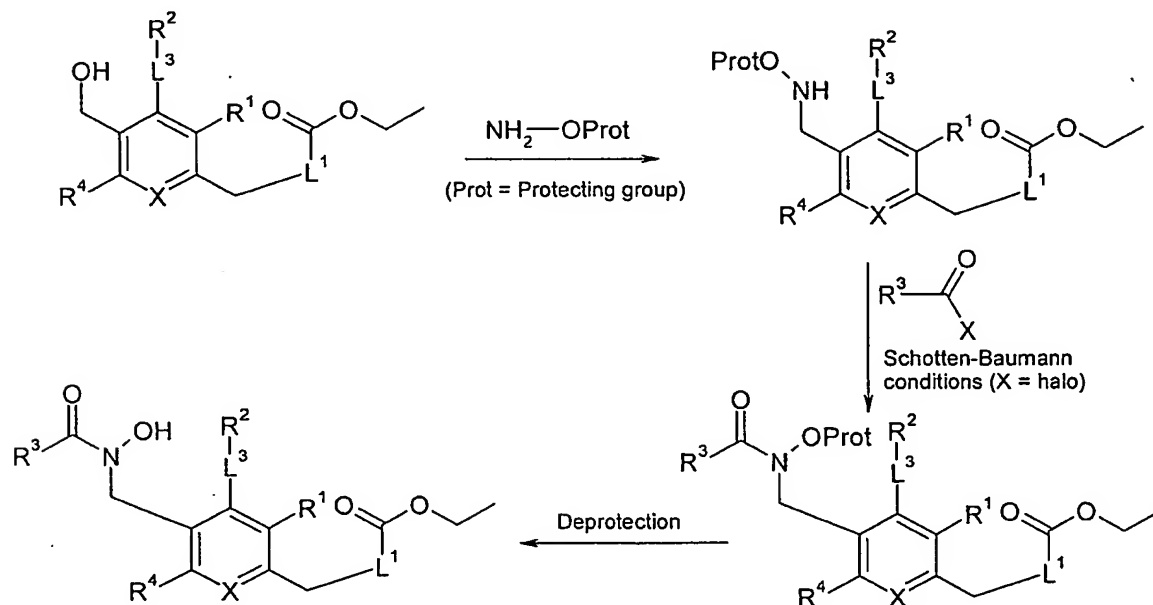
As an alternative to the substitution of the doubly  
 10 protected amine group at the position *meta* to the  $\text{X}$  group in  
 scheme 3, a singly protected amine group may be substituted  
 in the same position. In this case the group *meta* to the  $\text{X}$   
 group on the heterocyclic compound may be an  $\text{-OTs}$  group (as  
 in scheme 3) or may alternatively be an  $\text{-OH}$  group. This  
 15 general reaction is shown in scheme 4 below. In either  
 case, the reaction may proceed by reaction with a singly  
 protected amine group. Subsequent substitution of the amine

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-H group with  $R^3C(=O)X$  may then be achieved as shown in scheme 3 followed by deprotection of the amine groups to leave -OH attached to the amine N atom.

5

Scheme 4



In scheme 4 above, the protecting group may be any suitable protecting group such as acetyl, allyl, alloc, BOM, benzyl, benzoyl, DMPM, Fmoc, MEM, MOM, MPM, PMB, PMP, SEM, TBDMS, TBDPS, TBS, THP, TIPS, TMS, trityl or tosyl.

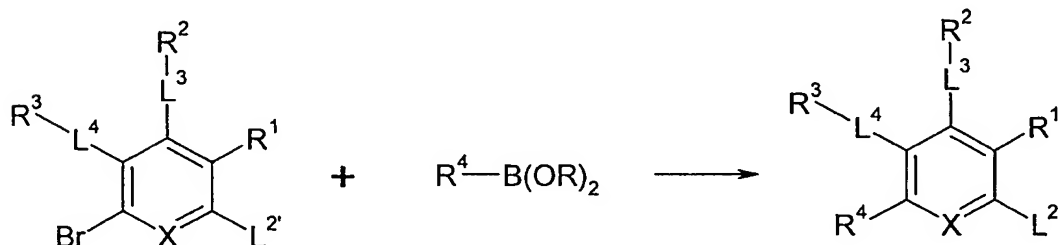
In general, the group  $R^1$  can be derived using standard reactions for the conversion of aryl substituent groups, including alkylation, reduction and substitution.

If  $R^3$  and  $R^4$  form a fused ring, then this would be present in the starting materials of a synthesis route to the compounds of the present invention.

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When  $R^4$  is an aryl or heterocyclyl group, this may be introduced to the compound by means of Suzuki coupling, i.e. by the coupling of an aryl halide to an organoboron derivative (scheme 5, wherein  $L^{2'}$  indicates  $-L^2-S-L^1-CO_2H$  or a precursor or protected form thereof and R is aryl or alkyl):

Scheme 5



A similar approach may be used to couple  $R^3$  and  $R^2$  to the central ring, when  $L^4$  and  $L^3$  respectively are single bonds. Furthermore, if  $R^2$  or  $R^3$  are aryl groups, the appropriate aryl halides may be coupled to boron derivatives of the remainder of the compound.

Certain compounds of the present invention are commercially available or can be derived from such compounds.

#### Preferences

The following preferences may be combined with one another, and may be different for each aspect of the present invention.

$R^1$  is preferably H, cyano, methyl, halo, hydroxy, hydroxamic acid, methoxy, amino, methylamino, dimethylamino, nitro, sulfhydryl, or methyl sulfide.

More preferably  $R^1$  is cyano, H or hydroxamic acid.

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Preferably  $L^1$  is phenylene, methylene, ethylene,  $-\text{CH}(\text{CH}_3)-$ ,  $-\text{CH}(\text{}^i\text{Pr})-$ ,  $-\text{CH}(\text{Ph})-$ ,  $-\text{CH}_2\text{-phenylene-}$ ,  $-\text{CH}_2\text{C(=O)NHCH}_2-$  or  $-\text{CH}_2\text{C(=O)NH-phenylene-}$ .

5

Preferably  $L^2$  is a single bond or  $-\text{C(=O)CH}_2-$ .

Preferably  $L^3$  is a single bond,  $-\text{L}^9\text{YN(OH)C(=O)L}^{10}-$  or  $-\text{L}^9\text{C(=O)N(OH)YL}^{10}-$ , wherein  $L^9$  and  $L^{10}$  are independently  
10 selected from optionally substituted  $\text{C}_{1-4}$  alkylene,  $\text{C}_{5-6}$  arylene,  $\text{C}_{1-4}$  alkylene- $\text{C}_{5-6}$  arylene and a single bond, and wherein Y is NH or a single bond.

Preferably  $L^4$  is a single bond,  $-\text{L}^9\text{YN(OH)C(=O)L}^{10}-$  or  
15  $-\text{L}^9\text{C(=O)N(OH)YL}^{10}-$ , wherein  $L^9$  and  $L^{10}$  are independently selected from optionally substituted  $\text{C}_{1-4}$  alkylene,  $\text{C}_{5-6}$  arylene,  $\text{C}_{1-4}$  alkylene- $\text{C}_{5-6}$  arylene and a single bond, and wherein Y is NH or a single bond.

20 For example,  $L^3$  or  $L^4$  may be a single bond,  $-\text{CH}_2\text{N(OH)C(=O)-}$ ,  $-\text{phenylene-CH}_2\text{N(OH)C(=O)-}$ ,  $-\text{phenylene-NHN(OH)C(=O)-}$ , or  $-\text{CH}_2\text{C(=O)N(OH)-}$ .

When X is CH, preferably one or more of  $R^1$ ,  $R^2$  and  $R^4$  are H.  
25 More preferably two of  $R^1$ ,  $R^2$  and  $R^4$  are H, when X is CH. It is most preferred that all of  $R^1$ ,  $R^2$  and  $R^4$  are H, when X is CH.

When X is CH, preferably one of  $R^2$  and  $R^3$  is optionally  
30 substituted  $\text{C}_{5-6}$  aryl,  $\text{C}_{3-7}$  cycloalkyl or  $\text{C}_{5-7}$  heterocyclyl. More preferably, when X is CH,  $R^3$  is optionally substituted  $\text{C}_{5-6}$  aryl,  $\text{C}_{3-7}$  cycloalkyl or  $\text{C}_{5-7}$  heterocyclyl. It is most preferred that when X is CH,  $R^3$  is optionally substituted

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phenyl or C<sub>3-7</sub> cycloalkyl. For example, R<sup>3</sup> may be phenyl or cyclopentyl.

When X is CH, preferably L<sup>1</sup> is phenylene or -CH(Ph)-.

5

When X is CH, preferably one of L<sup>3</sup> and L<sup>4</sup> is a single bond. More preferably, when X is CH, L<sup>3</sup> is a single bond.

When X is CH, preferably one of L<sup>3</sup> and L<sup>4</sup> is

10 -L<sup>9</sup>YN(OH)C(=O)L<sup>10</sup>- or -L<sup>9</sup>C(=O)N(OH)YL<sup>10</sup>-, wherein L<sup>9</sup> and L<sup>10</sup> are independently selected from optionally substituted C<sub>1-4</sub> alkylene, C<sub>5-6</sub> arylene, C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene and a single bond, and wherein Y is NH or a single bond. More preferably, when X is CH, L<sup>4</sup> is -L<sup>9</sup>YN(OH)C(=O)L<sup>10</sup>- or -L<sup>9</sup>C(=O)N(OH)YL<sup>10</sup>-,  
15 wherein L<sup>9</sup> and L<sup>10</sup> are independently selected from optionally substituted C<sub>1-4</sub> alkylene, C<sub>5-6</sub> arylene, C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene and a single bond, and wherein Y is NH or a single bond.

20 When X is N, R<sup>1</sup> is preferably CN or hydroxamic acid.

When X is N, R<sup>2</sup> is preferably selected from optionally substituted C<sub>5-6</sub> aryl, C<sub>5-7</sub> heterocyclyl, CF<sub>3</sub> and, together with R<sup>3</sup>, an optionally substituted butylene group wherein L<sup>3</sup>  
25 and L<sup>4</sup> are single bonds thus forming a C<sub>6</sub> ring fused with the aromatic ring to which L<sup>3</sup> and L<sup>4</sup> are attached.

When X is N, R<sup>2</sup> is more preferably selected from optionally substituted C<sub>5-6</sub> aryl and C<sub>5-7</sub> heterocyclyl.

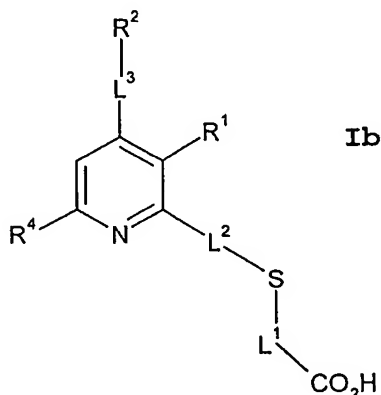
30

When X is N, R<sup>2</sup> is even more preferably optionally substituted phenyl or thiophenyl. For example, when X is N, R<sup>2</sup> may be thiophenyl, phenyl, p-chlorophenyl, p-

- 45 -

methoxyphenyl, *o*-methoxyphenyl, *p*-fluorophenyl. When X is N and R<sup>2</sup> is a monosubstituted phenyl, it is preferred that R<sup>2</sup> is a parasubstituted phenyl.

- 5 When X is N preferably R<sup>3</sup> is H or, together with R<sup>2</sup>, an optionally substituted butylene group wherein L<sup>3</sup> and L<sup>4</sup> are single bonds thus forming a C<sub>6</sub> ring fused with the aromatic ring to which L<sup>3</sup> and L<sup>4</sup> are attached.
- 10 When X is N, it is more preferable that R<sup>3</sup> is H and L<sup>4</sup> is a single bond such that the compounds of the invention are of formula Ib.



15

- When X is N, R<sup>4</sup> is preferably selected from optionally substituted C<sub>5-6</sub> aryl and C<sub>5-7</sub> heterocyclyl. When X is N, R<sup>4</sup> is more preferably optionally substituted phenyl, thiophenyl, furanyl or pyridyl. For example, when X is N R<sup>4</sup> may be phenyl, *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl, *p*-fluorophenyl, thiophenyl, furanyl or pyridyl. When X is N and R<sup>4</sup> is a monosubstituted phenyl, it is preferable that R<sup>4</sup> is a parasubstituted phenyl. When X is N and R<sup>4</sup> is a disubstituted phenyl, it is preferred that the
- 25 substituents are in the *meta* and *para* positions.

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When  $R^2$ ,  $R^3$  or  $R^4$  is a substituted  $C_{5-6}$  aryl group, preferred substituents are halo,  $C_{1-4}$  alkyl or  $-OR$ , wherein  $R$  is  $C_{1-4}$  alkyl. When  $R^2$ ,  $R^3$  or  $R^4$  is a monosubstituted phenyl group it is preferred that the substituent is in the *para* position. When  $R^2$ ,  $R^3$  or  $R^4$  is a disubstituted phenyl group it is preferred that the substituents are in the *para* and *meta* positions. For example  $R^2$ ,  $R^3$  and  $R^4$  may be *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl, *p*-fluorophenyl.

When compounds of formula I have at least one  $-C(=O)N(OH)-$  group, preferably at least one of  $R^1$ ,  $L^3$  or  $L^4$  comprises a  $-C(=O)N(OH)-$  group. Preferably  $L^4$  comprises a  $-C(=O)N(OH)-$  group.

When compounds of formula I have at least one  $-C(=O)N(OH)-$  group, it is preferable that  $L^4$  is a  $L^9-C(=O)N(OH)-$  group where preferably  $L^9$  is selected from  $C_{1-4}$  alkylene and  $C_{5-6}$  arylene and most preferably  $L^9$  is phenyl.

When compounds of formula I have at least one  $-C(=O)N(OH)-$  group, it is preferable that  $X$  is  $CH$ .

When compounds of formula I have at least one  $-C(=O)N(OH)-$  group, preferably at least one, more preferably at least two of  $R^1$ ,  $R^2$  and  $R^4$  is  $H$ . Most preferably all of  $R^1$ ,  $R^2$  and  $R^4$  are  $H$ .

When compounds of formula I have at least one  $-C(=O)N(OH)-$  group,  $R^3$  is preferably  $C_{5-6}$  aryl and more preferably  $R^3$  is phenyl.

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When compounds of formula I have at least one  $-C(=O)N(OH)-$  group,  $R^6$  is preferably H or  $C_{1-7}$  alkyl and is more preferably  $C_{1-3}$  alkyl.

- 5 When compounds of formula I have at least one  $-C(=O)N(OH)-$  group,  $L^1$  is preferably phenylene,  $-CH(Ph)-$ ,  $-CH_2$ -phenylene- or  $-CH_2C(=O)NH$ -phenylene-.

10 When compounds of formula I have at least one  $-C(=O)N(OH)-$  group,  $L^2$  is preferably a single bond or  $-C(=O)CH_2-$ .

When compounds of formula I have at least one  $-C(=O)N(OH)-$  group,  $L^3$  is preferably a single bond.

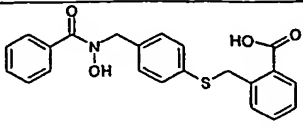
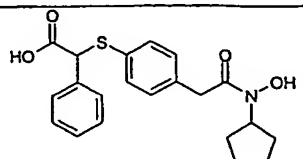
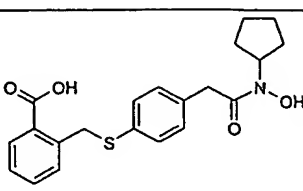
- 15 Particularly preferred compounds include those listed in tables 1 and 4.

Table 1

Compound	Structure
A	
B	
C	
D	



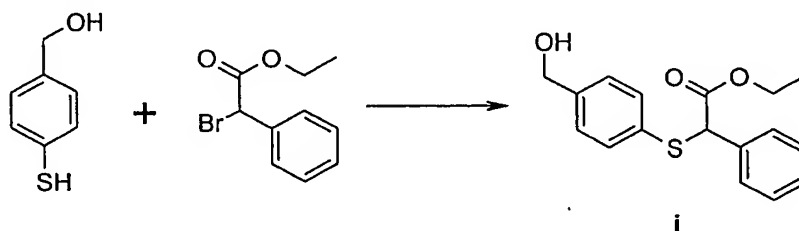
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E	
F	
G	

Examples

**Example 1: Formation of {4-[(Benzoyl-hydroxy-amino)-methyl]-phenylsulfanyl}-phenyl-acetic acid ethyl ester (iv)**

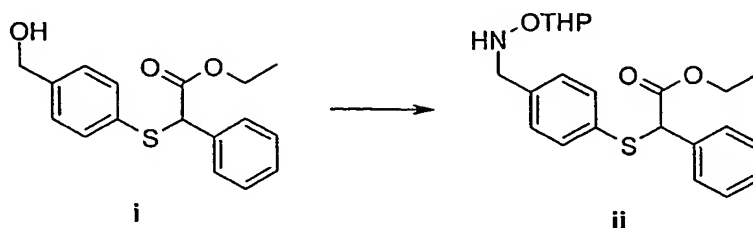
- 5 Step 1 - (4-Hydroxymethyl-phenylsulfanyl)-phenyl-acetic acid ethyl ester (i)



- 10 4-Mercaptobenzyl alcohol (0.582g, 0.0042mol), ethyl alpha bromophenyl acetate (0.727 ml, 0.0042mol) and potassium carbonate (0.86g, 0.0062 mol, 1.5 eq) were refluxed in acetone (25 ml) for 12 h. The crude material was purified by flash column chromatography (Ethyl acetate/hexane) to give the product i as a yellow oil (0.79g, 63%).

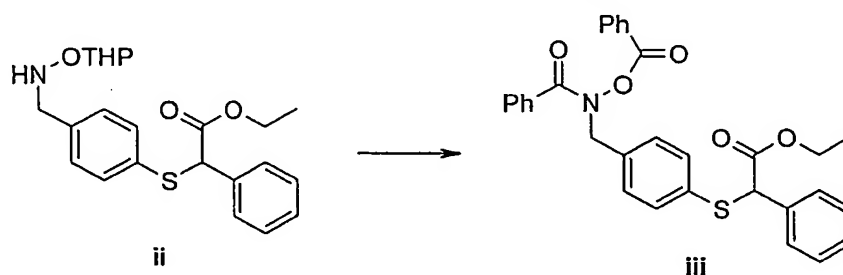
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Step 2 - (4-Methylaminomethyl-phenylsulfanyl)-phenyl-acetic acid ethyl ester (ii)



5 Trifluoroacetic anhydride (0.4ml, 0.002 mol) was added to a solution of **i** (0.65g, 0.002mol) in dichloromethane at 0°C under nitrogen. After 5 min lutidine (0.29 ml, 0.0024 mol) was added and the solution stirred for a further 5 min. O-Tetrahydro-2H-pyran-2-yl-hydroxylamine (0.5g, 0.004 mol,  
10 2eq) was added and the cooling removed. The reaction was stirred at room temperature overnight. The required product was isolated following flash column chromatography yielding **ii** (362mg, 42%),  $m/z$  [ES] 402  $[M+H]^+$  424  $[M+Na]^+$

15 Step 3 - (4-[(Benzoyl-benzoyloxy-amino)-methyl]-phenylsulfanyl)-phenyl-acetic acid ethyl ester (iii)

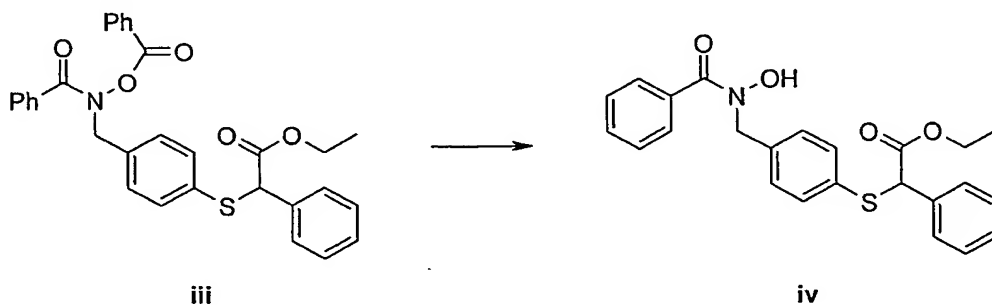


To a solution of **ii** (362mg, 0.9 mmol) and triethylamine  
20 (0.19ml, 1.5 eq) in dichloromethane (30 ml) was added benzoyl chloride (0.16 ml, 1.5 eq). This was allowed to stir at room temperature for 2 h. The solvent was removed *in situ* and the product purified by flash column

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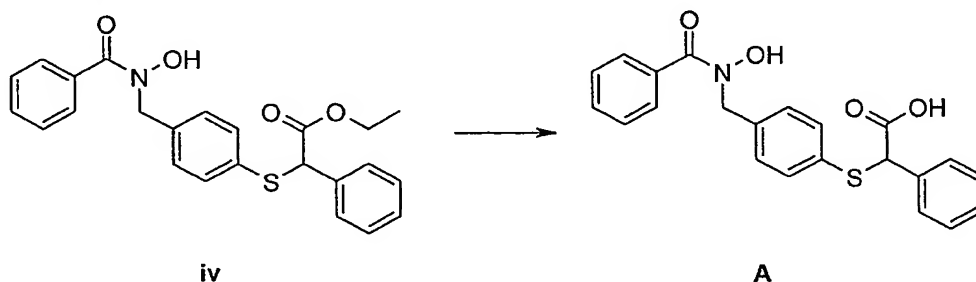
chromatography (EtOAc/hexane). The unexpected compound **iii** was recovered (0.147g, 31%) as a colourless oil,  $m/z$  [ES] 548  $[M+Na]^+$

5 **Step 4 - {4-[(Benzoyl-hydroxy-amino)-methyl]-phenylsulfanyl}-phenyl-acetic acid ethyl ester (iv)**



To a solution of **iii** (0.144g, 0.27mmol) in dichloromethane  
10 (10 ml) was added polymer supported trisamine (2.46 mmol/g, 0.33g, 0.82mmol, 3eq). The reaction was stirred at room temperature for 72 h. The resin was filtered off and the residue concentrated *in vacuo*. The crude material was purified by prep HPLC to yield the required product (**iv**)  
15 (47mg, 41%).  $^1H$  NMR (400 MHz, MeOD- $d_4$ )  $\delta$ : 7.7-7.1 (14H, Ar), 4.95 (1H, s), 4.75 (2H, m,  $CH_2$ ), 3.95 (2H, m), 0.95 (3H, t),  $m/z$  [ES] 422  $[M+H]^+$

20 **Example 2: Formation of {4-[(Benzoyl-hydroxy-amino)-methyl]-phenylsulfanyl}-phenyl-acetic acid (A)**



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To a solution of **iv** (0.079g, 0.19mmol) in THF/water (6ml/2ml) was added sodium hydroxide (0.47mmol, 2.5eq). The reaction was stirred at room temperature for 16 h. The solution was neutralized with 1M HCl (0.11ml) and the solvent removed *in vacuo*. The crude material was purified by prep HPLC to yield the required product (**A**) (4.1mg, 6%).

<sup>1</sup>H NMR (400 MHz, MeOD-d<sub>4</sub>)  $\delta$ : 7.7-7.1 (14H, Ar), 4.9 (1H, s), 4.75 (2H, m, CH<sub>2</sub>), m/z [ES] 394 [M+H]<sup>+</sup>

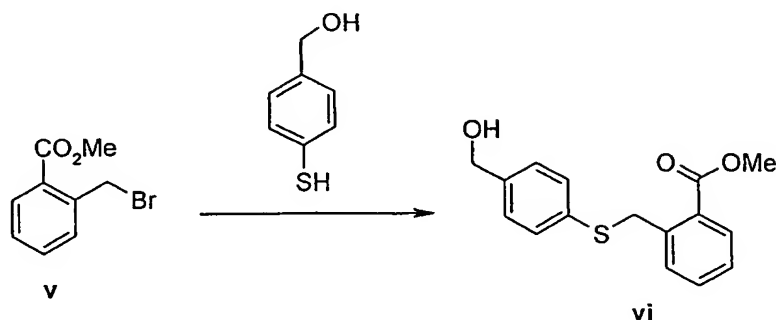
**Example 3: Formation of 2-{4-[(Benzoyl-hydroxy-amino)-methyl]-phenylsulfanylmethyl}-benzoic acid methyl ester**  
Step 1 - 2-Bromomethyl-benzoic acid methyl ester



To a solution of methyl 2-methylbenzoate (5g, 0.033mol) in carbon tetrachloride (85ml) was added n-bromosuccinimide (5.93g, 0.033mol) and benzoyl peroxide (0.22g, 0.9mol). The reaction was refluxed for 4 hr. The reaction was cooled to room temperature. The white precipitate was filtered and the solvent removed. The oil was dissolved in Et<sub>2</sub>O and cooled to -78°C The product precipitated and collected yielding **v** (5.86g, 77%).

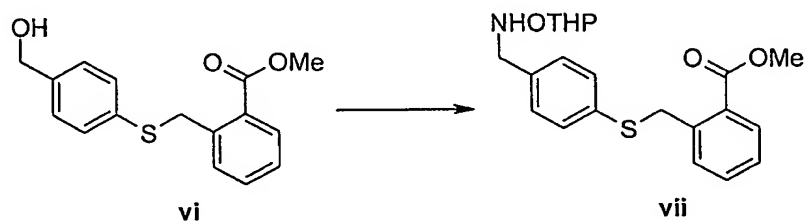
- 52 -

Step 2 - 2-(4-Hydroxymethyl-phenylsulfanylmethyl)-benzoic acid methyl ester



5 4-Mercaptobenzyl alcohol (0.579g, 0.0041mol), methyl 2-bromomethyl benzoate (**v**) (0.946, 0.0041mol) and potassium carbonate (0.85g, 0.0062 mol, 1.5 eq) were refluxed in acetone (25 ml) for 12 h. The crude material was purified by flash column chromatography (ethyl acetate/hexane) to  
 10 give the product **vi** as a colourless oil (0.855g, 72%), m/z [ES] 311 [M+Na]<sup>+</sup>

Step 3 - 2-(4-[(Tetrahydro-pyran-2-yloxyamino)-methyl]-phenylsulfanylmethyl)-benzoic acid methyl ester



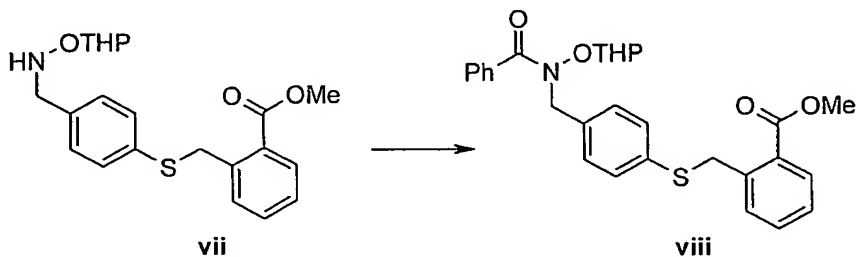
15

Trifluoroacetic anhydride (0.91ml, 0.005mol) was added to a solution of **vi** (1.41g, 0.005mol) in dichloromethane at 0°C under nitrogen. After 5 min lutidine (0.66 ml, 0.56mol) was  
 20 added and the solution stirred for a further 5 min. O-Tetrahydro-2H-pyran-2-yl-hydroxylamine (1.15g, 0.0098 mol, 2eq) was added dropwise and the reaction stirred for 30 minutes. The required product was isolated following prep

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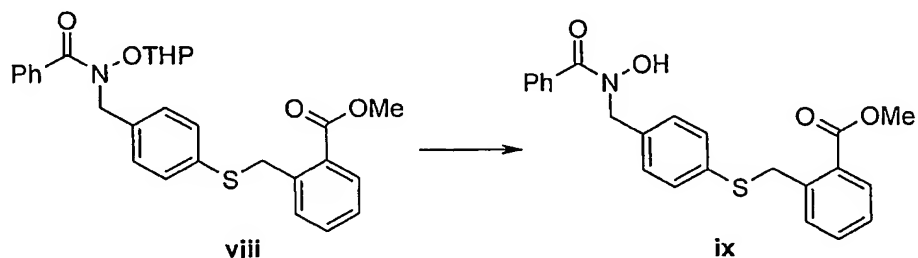
HPLC yielding **vii** (0.114g, 6%),  $m/z$  [ES] 388  $[M+H]^+$  410  $[M+Na]^+$

Step 4 - 2-(4-([Benzoyl-(tetrahydro-pyran-2-yloxy)-amino]-methyl)-phenylsulfanylmethyl)-benzoic acid methyl ester



To a solution of **vii** (114mg, 0.29 mmol) and diisopropylethylamine (0.19ml, 1.5 eq) in dichloromethane (30 ml) was added benzoyl chloride (0.04 ml, 1.2 eq). This was allowed to stir at room temperature for 1 h. The reaction was quenched with aqueous  $\text{NaHCO}_3$  (1 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (EtOAc/hexane). The required product **viii** was recovered (96.5mg, 67%) as a colourless oil,  $m/z$  [ES] 492  $[M+H]^+$ , 514  $[M+Na]^+$

Step 5 - 2-(4-[(Benzoyl-hydroxy-amino)-methyl]-phenylsulfanylmethyl)-benzoic acid methyl ester



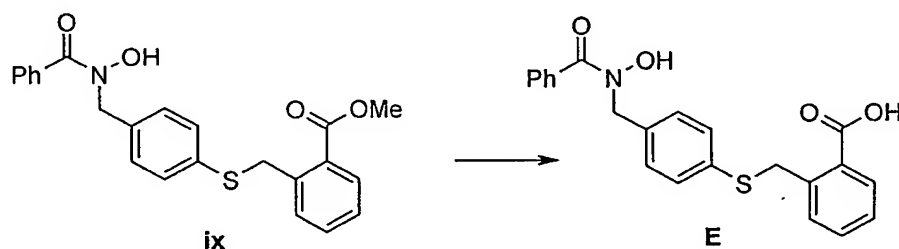
Compound **viii** (68.2 mg, 0.14mmol) was stirred with (TFA/ $\text{H}_2\text{O}$ /DCM, 2.5:1:96.5, 10 ml) at room temperature and

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monitored by LC-MS (reaction was complete ~ 3 h). The reaction mixture was quenched with aqueous NaHCO<sub>3</sub>. The phases were separated and the organic layer concentrated in vacuo after drying. Compound ix required no further

5 purification (97% LC-MS). <sup>1</sup>H NMR (400 MHz, MeOD-d<sub>4</sub>) δ: 7.75 (1H, d, Ar), 7.5-7.6 (2H, m, Ar), 7.45-7.1 (10H, m, Ar), 4.75 (2H, m), 4.4 (2H, s), 3.75 (3H, s), m/z [ES] 408 [M+H]<sup>+</sup>.

10 **Example 4: Formation of 2-{4-[(Benzoyl-hydroxy-amino)-methyl]-phenylsulfanylmethyl}-benzoic acid (E)**



To a solution of ix (60 mg, 0.15 mmol) in MeOH/water (4 ml/2 ml) was added NaOH (0.22 ml, 1M solution, 0.22 mmol) and the reaction stirred at room temperature for 6 days. After this time 60% conversion to product was observed. The required product was isolated following prep HPLC yielding the required product (E) as a white solid (7mg, 12%). <sup>1</sup>H NMR

20 (400 MHz, MeOD-d<sub>4</sub>) δ: 7.85 (1H, m, Ar), 7.5-7.6 (2H, m, Ar), 7.45-7.1 (10H, m, Ar), 4.75 (2H, m), 4.45 (2H, s), m/z [ES] 394 [M+H]<sup>+</sup>.

**Example 5: Glyoxalase I inhibition assay**

25 Glyoxalase I catalyses the formation of S-D-lactoylglutathione from the hemithioacetal that forms non-enzymatically from methylglyoxal and reduced glutathione (GSH). The standard literature assay is a cuvette-based

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spectrophotometric method using the product of glyoxalase I, S-D-lactoylglutathione, as the chromophore (240 nm) (Racker, *J. Biol. Chem.* **190**, 685-686 (1951); Principato et al., *Biochem International* **6**, 249-255 (1983)). This literature  
5 method was modified for use as a 96-well plate, kinetic assay.

The buffer (0.1M potassium phosphate buffer pH 6.6) and inhibitors are added to appropriate wells of a 96 well  
10 plate. Methylglyoxal (prepared in potassium phosphate buffer pH 6.6) and reduced glutathione (prepared in potassium phosphate buffer pH 6.6) are added to appropriate wells. These reagents are incubated for 15 minutes, shaking at room temperature to allow the formation of the  
15 hemithioacetal substrate of glyoxalase I. Recombinant human glyoxalase I (expressed in *E. coli*. and purified by S-hexylglutathione-agarose chromatography as described in Ridderstorm M. and Mannervik B., *Biochem J.* **314**, 463-467 (1996)) is added and the plate is shaken briefly, before  
20 being placed in a Spectra Max 190 microplate spectrophotometer (Molecular Devices) at 25°C. Absorbance is monitored at 240 nm, with readings being taken every 30 seconds. The reaction is monitored for 15 minutes and PathCheck® measurements are taken on completion of the assay  
25 and the absorbance values normalized to a 1 cm pathlength. The integral software determines the Vmax using the first 20 readings. S-hexylglutathione is used as a positive control in the assays.

30 Data are expressed as a percentage of the control Vmax, measured in the absence of inhibitor.

Compounds **iv**, **A**, **ix** and **E** from examples 1 to 4 above



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respectively were subjected to the above glyoxalase I binding assay at a concentration of 20 $\mu$ M (20 micromolar). Inhibitory effects are expressed in table 2 as either IC<sub>50</sub> values, defined as the concentration, in  $\mu$ M, of the compound that results in 50% of the vehicle control response, or as the percentage of the vehicle control response at the highest concentration of compound tested.

Compound	% inhibition at 20 $\mu$ M	IC <sub>50</sub> ( $\mu$ M)
<b>iv</b>	28.5	
<b>A</b>		9.7
<b>ix</b>	0	
<b>E</b>		1.9-2.26

Table 2

The results in table 2 show that compounds **A** and **E** exhibit good glyoxalase I inhibition, i.e. have low IC<sub>50</sub> values, whereas the corresponding ethyl and methyl esters, **iv** and **ix** respectively, show relatively low % inhibition of glyoxalase I activity. This indicates that the ester forms of these compounds do not inhibit glyoxalase I as well as the free forms so indicating the suitability of the ester forms as a prodrug.

#### Example 6: HL60 Cell Assay

HL60 (human promyelocytic leukaemia) cells were seeded (50 $\mu$ l/well) at a density between 0.25-0.4 x 10<sup>5</sup>/ml in a 96 multi-well plate. Twenty four hours later 50 $\mu$ l. of the relevant compound dilution made up in culture medium was added to the wells (final concentration range 20-1.25 $\mu$ M in 0.1%DMSO). After incubating at 37°C in a 5% CO<sub>2</sub> atmosphere for a further 72 hours, assessment of growth inhibitory

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effects of compounds was measured using a colorimetric assay that is based on the cleavage of the tetrazolium salt WST-1 (Roche) by mitochondrial dehydrogenase in viable cells.

WST-1 reagent (10 $\mu$ l) was added to each well and the plate

5 was agitated for 1 min. After a 3-4 hour incubation at 37°C in a 5% CO<sub>2</sub> incubator the absorbance at 450nm was read spectrophotometrically, after subtraction of a reference wavelength absorbance, at 690nm.

10 Compounds **iv**, **ix** and **E** from examples 1, 3 and 4 above respectively were subjected to the above cell assay. Results were the mean of six replicates and were expressed as the percentage of the DMSO vehicle control response. Inhibitory effects are expressed in table 3 in the form of  
15 either IC<sub>50</sub> values, which was defined as the concentration ( $\mu$ M) of compound that results in 50% of the vehicle control response, or as the % of vehicle control response at the highest concentration of compound tested.

Compound	% proliferation inhibition in HL60s	IC <sub>50</sub> ( $\mu$ M)
<b>iv</b>	80	8.3
<b>ix</b>		15
<b>E</b>	4	

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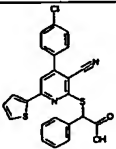
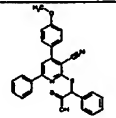
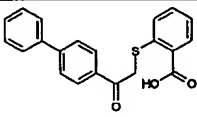
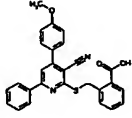
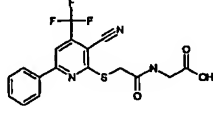
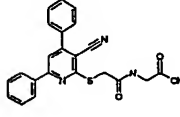
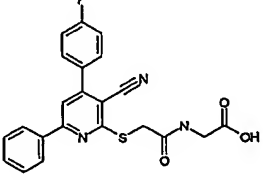
Table 3

Without wishing to be bound by theory, the significant activity of the ester compounds **iv** and **ix** in the HL60 assay, shown in table 3, indicates that the ester compounds may be  
25 converted into active form in cell culture hence demonstrating their suitability for use as prodrug compounds.

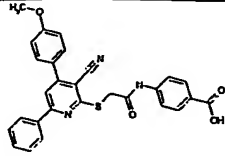
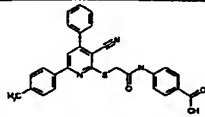
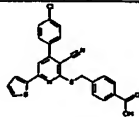
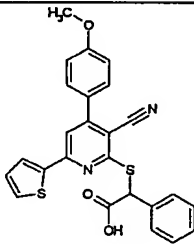
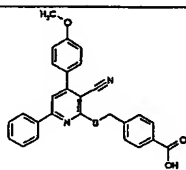
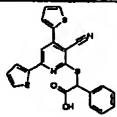
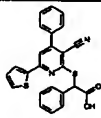
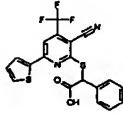
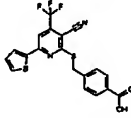
**Example 7 - Glyoxalase binding assay of commercially available compounds.**

The compounds of table 4 were obtained from commercial sources.

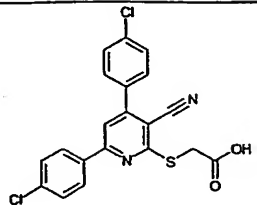
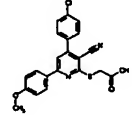
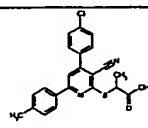
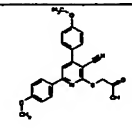
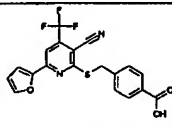
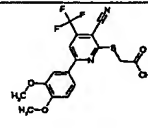
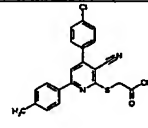
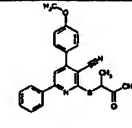
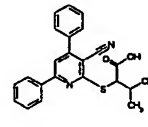
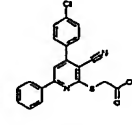
Table 4

Compound	Structure
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Various compounds from table 4 were subjected to the above glyoxalase I binding assay at a concentration of 20  $\mu$ M (20 micromolar) as described in example 5. The following

5 compounds exhibited inhibition, at 20  $\mu$ M, of 30% or above:

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1, 2, 3, 4, 9, 11, 13, 14, 25.

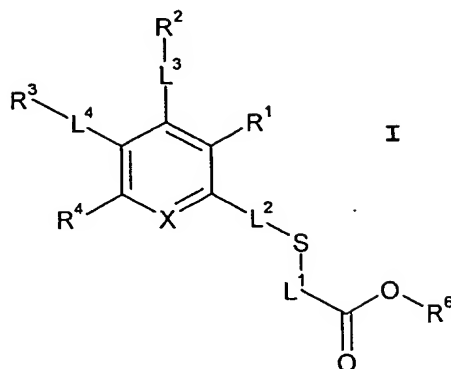
**Example 8 - HL60 assay of 2-(2-Biphenyl-4-yl-2-oxo-ethylsulfanyl)-benzoic acid (compound 3).**

- 5 The ethyl ester of compound 3 in table 4 was obtained from commercial sources and was also tested using the HL60 assay as described in example 6. This compound exhibited a 72% inhibition of proliferation in HL60s and had an  $IC_{50}$  value of 7.5 $\mu$ M.

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Claims

1. A compound of formula I:



wherein

5 X is N or CH;

$R^1$  is H, cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or  $-NH_2$ ; or  $C_{1-4}$  alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or  $-NH_2$ ; or  $-OR$ ,  $-NHR$ ,  $-NR_2$  or  $-SR$  wherein R is  $C_{1-4}$  alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or  $-NH_2$ ;

$R^2$  is H,  $CF_3$ ; or optionally substituted  $C_{5-6}$  aryl,  $C_{3-7}$  cycloalkyl,  $C_{5-7}$  heterocyclyl or together with  $R^3$  an optionally substituted  $C_{3-4}$  alkylene group wherein  $L^3$  and  $L^4$  are single bonds thus forming a  $C_{5-6}$  ring fused with the aromatic ring to which  $L^3$  and  $L^4$  are attached;

$R^3$  is H; or optionally substituted  $C_{5-6}$  aryl,  $C_{3-7}$  cycloalkyl,  $C_{5-7}$  heterocyclyl or together with  $R^2$  an optionally substituted  $C_{3-4}$  alkylene group wherein  $L^3$  and  $L^4$  are single bonds thus forming a  $C_{5-6}$  ring fused with the aromatic ring to which  $L^3$  and  $L^4$  are attached;

$R^4$  is H; or optionally substituted  $C_{5-6}$  aryl or  $C_{5-7}$  heterocyclyl;

$R^6$  is selected from H or optionally substituted  $C_{1-7}$  alkyl,  $C_{5-6}$  aryl and  $C_{1-4}$  alkylene- $C_{5-6}$  aryl;

$L^1$  is optionally substituted  $C_{1-4}$  alkylene,  $C_{5-6}$  arylene,



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C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene or -L<sup>5</sup>N(R<sup>5</sup>)L<sup>6</sup>-, wherein L<sup>5</sup> and L<sup>6</sup> are independently selected from optionally substituted C<sub>1-4</sub> alkylene and C<sub>5-6</sub> arylene, and R<sup>5</sup> is H or C<sub>1-4</sub> alkyl;

5 L<sup>2</sup> is a single bond; or optionally substituted C<sub>1-4</sub> alkylene or -L<sup>7</sup>C(=O)L<sup>8</sup>-, wherein L<sup>7</sup> and L<sup>8</sup> are independently selected from optionally substituted C<sub>1-4</sub> alkylene and a single bond; and

10 L<sup>3</sup> and L<sup>4</sup> are independently selected from a single bond, optionally substituted C<sub>1-4</sub> alkylene, -L<sup>9</sup>YN(OH)C(=O)L<sup>10</sup>- and -L<sup>9</sup>C(=O)N(OH)YL<sup>10</sup>-, wherein L<sup>9</sup> and L<sup>10</sup> are independently selected from optionally substituted C<sub>1-4</sub> alkylene, C<sub>5-6</sub> arylene, C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene and a single bond, wherein Y is NH or a single bond; or a pharmaceutically acceptable salt thereof for use in a  
15 method of therapy.

2. A compound according to claim 1 wherein R<sup>1</sup> is chosen from the group consisting of H and cyano.

20 3. A compound according to any one of the preceding claims wherein R<sup>6</sup> is H or C<sub>1-7</sub> alkyl.

4. A compound according to any one of the preceding claims wherein L<sup>1</sup> is chosen from the group consisting of  
25 phenylene, -CH(Ph)-, -CH<sub>2</sub>-phenylene- and -CH<sub>2</sub>C(=O)NH-phenylene-.

5. A compound according to any one of the preceding claims wherein L<sup>2</sup> is a single bond or -C(=O)CH<sub>2</sub>-.  
30

6. A compound according to any one of the preceding claims wherein L<sup>3</sup> is chosen from the group consisting of a single bond, -L<sup>9</sup>YN(OH)C(=O)L<sup>10</sup>- and -L<sup>9</sup>C(=O)N(OH)YL<sup>10</sup>-,

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wherein  $L^9$  and  $L^{10}$  are independently selected from optionally substituted  $C_{1-4}$  alkylene,  $C_{5-6}$  arylene,  $C_{1-4}$  alkylene- $C_{5-6}$  arylene and a single bond, and wherein Y is NH or a single bond.

5

7. A compound according to claim 6 wherein  $L^3$  is a single bond.

8. A compound according to any one of the preceding  
10 claims wherein  $L^4$  is chosen from the group consisting of a single bond,  $-L^9YN(OH)C(=O)L^{10}-$  and  $-L^9C(=O)N(OH)YL^{10}-$ , wherein  $L^9$  and  $L^{10}$  are independently selected from optionally substituted  $C_{1-4}$  alkylene,  $C_{5-6}$  arylene,  $C_{1-4}$  alkylene- $C_{5-6}$  arylene and a single bond, and wherein Y is NH or a single  
15 bond.

9. A compound according to claim 8 wherein  $L^4$  is selected from the group consisting of  $-CH_2N(OH)C(=O)-$ ,  $-phenylene-CH_2N(OH)C(=O)-$ ,  $-phenylene-NHN(OH)C(=O)-$  and  
20  $-CH_2C(=O)N(OH)-$ .

10. A compound according to any one of the preceding claims wherein X is CH.

25 11. A compound according to claim 10 wherein one of  $R^1$ ,  $R^2$  and  $R^4$  are H.

12. A compound according to claim 10 wherein two of  $R^1$ ,  $R^2$  and  $R^4$  are H.

30

13. A compound according to claim 10 wherein  $R^1$ ,  $R^2$  and  $R^4$  are all H.

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14. A compound according to claim 10 wherein one of R<sup>2</sup> and R<sup>3</sup> is optionally substituted C<sub>5-6</sub> aryl, C<sub>3-7</sub> cycloalkyl or C<sub>5-7</sub> heterocyclyl.

5 15. A compound according to claim 14 wherein R<sup>3</sup> is optionally substituted C<sub>5-6</sub> aryl, C<sub>3-7</sub> cycloalkyl or C<sub>5-7</sub> heterocyclyl.

10 16. A compound according to claim 14 wherein R<sup>3</sup> is optionally substituted phenyl or C<sub>3-7</sub> cycloalkyl.

17. A compound according to claim 14 wherein R<sup>3</sup> is phenyl or cyclopentyl.

15 18. A compound according to claim 10 wherein L<sup>1</sup> is phenylene or -CH(Ph)-.

19. A compound according to claim 10 wherein one of L<sup>3</sup> and L<sup>4</sup> is a single bond.

20

20. A compound according to claim 19 wherein L<sup>3</sup> is a single bond.

21. A compound according to any one of claims 1 to 9  
25 wherein X is N.

22. A compound according to claim 21 wherein R<sup>1</sup> is cyano or hydroxamic acid.

30 23. A compound according to claim 21 wherein R<sup>2</sup> is selected from the group consisting of optionally substituted C<sub>5-6</sub> aryl, C<sub>5-7</sub> heterocyclyl, CF<sub>3</sub> and, together with R<sup>3</sup>, an optionally substituted butylene group wherein L<sup>3</sup> and L<sup>4</sup> are

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single bonds thus forming a C<sub>6</sub> ring fused with the aromatic ring to which L<sup>3</sup> and L<sup>4</sup> are attached.

24. A compound according to claim 23 wherein R<sup>2</sup> is  
5 selected from optionally substituted C<sub>5-6</sub> aryl or C<sub>5-7</sub> heterocyclyl.

25. A compound according to claim 23 wherein R<sup>2</sup> is  
selected from optionally substituted phenyl or thiophenyl.

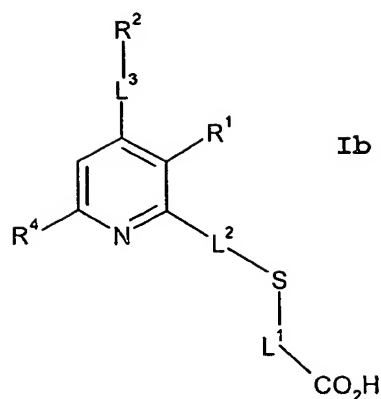
26. A compound according to claim 23 wherein R<sup>2</sup> is  
selected from the group consisting of thiophenyl, phenyl,  
p-chlorophenyl, p-methoxyphenyl, o-methoxyphenyl and  
p-fluorophenyl.

27. A compound according to any one of claims 23 to 25  
wherein R<sup>2</sup> is a monosubstituted phenyl group with the  
substituent group being in the para position.

28. A compound according to any one of claims 21 to 27  
wherein R<sup>3</sup> is H or, together with R<sup>2</sup>, an optionally  
substituted butylene group wherein L<sup>3</sup> and L<sup>4</sup> are single  
bonds thus forming a C<sub>6</sub> ring fused with the aromatic ring to  
which L<sup>3</sup> and L<sup>4</sup> are attached.

29. A compound according to claim 28 wherein R<sup>3</sup> is H and  
L<sup>4</sup> is a single bond such that the compound is of formula Ib:

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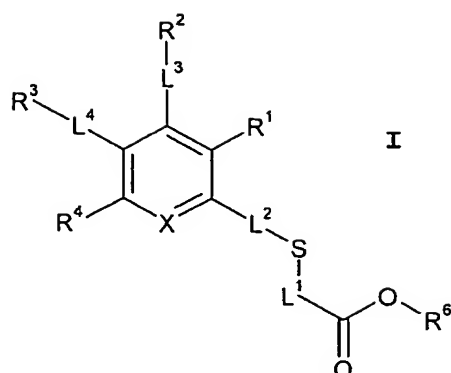
30. A pharmaceutical composition comprising a compound according to any one of the preceding claims or a  
5 pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

31. Use of a compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt thereof in the  
10 preparation of a medicament for the treatment of a condition alleviated by inhibition of glyoxalase I.

32. A method of treating a condition which can be alleviated by inhibition of glyoxalase I, which method  
15 comprises administering to a patient in need of treatment an effective amount of a compound according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof.

20 33. A compound of formula I:

- 69 -



or a salt, solvate or chemically protected form thereof  
wherein

X is N or CH;

- 5         $R^1$  is H, cyano, halo, hydroxy, hydroxamic acid,  
sulfhydryl or  $-NH_2$ ; or  $C_{1-4}$  alkyl optionally substituted by  
cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or  $-NH_2$ ;  
or  $-OR$ ,  $-NHR$ ,  $-NR_2$  or  $-SR$  wherein R is  $C_{1-4}$  alkyl optionally  
substituted by cyano, halo, hydroxy, hydroxamic acid,  
10    sulfhydryl or  $-NH_2$ ;

- $R^2$  is H,  $CF_3$ ; or optionally substituted  $C_{5-6}$  aryl,  $C_{3-7}$   
cycloalkyl,  $C_{5-7}$  heterocyclyl or together with  $R^3$  an  
optionally substituted  $C_{3-4}$  alkylene group wherein  $L^3$  and  $L^4$   
are single bonds thus forming a  $C_{5-6}$  ring fused with the  
15    aromatic ring to which  $L^3$  and  $L^4$  are attached;

- $R^3$  is H; or optionally substituted  $C_{5-6}$  aryl,  $C_{3-7}$   
cycloalkyl,  $C_{5-7}$  heterocyclyl or together with  $R^2$  an  
optionally substituted  $C_{3-4}$  alkylene group wherein  $L^3$  and  $L^4$   
are single bonds thus forming a  $C_{5-6}$  ring fused with the  
20    aromatic ring to which  $L^3$  and  $L^4$  are attached;

$R^4$  is H; or optionally substituted  $C_{5-6}$  aryl or  $C_{5-7}$   
heterocyclyl;

$R^6$  is selected from H or optionally substituted  $C_{1-7}$   
alkyl,  $C_{5-6}$  aryl and  $C_{1-4}$  alkylene- $C_{5-6}$  aryl;

- 25         $L^1$  is optionally substituted  $C_{1-4}$  alkylene,  $C_{5-6}$  arylene,  
 $C_{1-4}$  alkylene- $C_{5-6}$  arylene or  $-L^5N(R^5)L^6-$ , wherein  $L^5$  and  $L^6$

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are independently selected from optionally substituted C<sub>1-4</sub> alkylene and C<sub>5-6</sub> arylene, and R<sup>5</sup> is H or C<sub>1-4</sub> alkyl;

L<sup>2</sup> is a single bond; or optionally substituted C<sub>1-4</sub> alkylene or -L<sup>7</sup>C(=O)L<sup>8</sup>-, wherein L<sup>7</sup> and L<sup>8</sup> are independently  
5 selected from optionally substituted C<sub>1-4</sub> alkylene and a single bond; and

L<sup>3</sup> and L<sup>4</sup> are independently selected from a single bond, optionally substituted C<sub>1-4</sub> alkylene, -L<sup>9</sup>YN(OH)C(=O)L<sup>10</sup>- and -L<sup>9</sup>C(=O)N(OH)YL<sup>10</sup>-, wherein L<sup>9</sup> and L<sup>10</sup> are independently  
10 selected from optionally substituted C<sub>1-4</sub> alkylene, C<sub>5-6</sub> arylene, C<sub>1-4</sub> alkylene-C<sub>5-6</sub> arylene and a single bond, wherein Y is NH or a single bond; and  
wherein the compound contains at least one -C(=O)N(OH)- group.

15 34. A compound according to claim 33 wherein at least one of R<sup>1</sup>, L<sup>3</sup> or L<sup>4</sup> comprises a -C(=O)N(OH)- group.

20 35. A compound according to claim 33 wherein L<sup>4</sup> comprises a -C(=O)N(OH)- group.

36. A compound according to any one of claims 33 to 35 wherein L<sup>4</sup> is a L<sup>9</sup>-C(=O)N(OH)- group.

25 37. A compound according to claim 36 wherein L<sup>9</sup> is selected from C<sub>1-4</sub> alkylene and C<sub>5-6</sub> arylene.

38. A compound according to claim 36 wherein L<sup>9</sup> is methylene or phenylene.

30 39. A compound according to any one of claims 33 to 38 wherein X is CH.

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40. A compound according to any one of claims 33 to 39 wherein at least one of  $R^1$ ,  $R^2$  and  $R^4$  is H.

41. A compound according to any one of claims 33 to 39 wherein at least two of  $R^1$ ,  $R^2$  and  $R^4$  are H.

42. A compound according to any one of claims 33 to 39 wherein all of  $R^1$ ,  $R^2$  and  $R^4$  are H.

43. A compound according to any one of claims 33 to 42 wherein  $R^3$  is optionally substituted  $C_{5-6}$  aryl.

44. A compound according to claim 43 wherein  $R^3$  is phenyl.

45. A compound according to any one of claims 33 to 44 wherein  $R^6$  is H or  $C_{1-7}$  alkyl.

46. A compound according to claim 45 wherein  $R^6$  is H or  $C_{1-3}$  alkyl.

47. A compound according to any one of claims 33 to 46 wherein  $L^1$  is phenylene,  $-\text{CH}(\text{Ph})-$ ,  $-\text{CH}_2\text{-phenylene-}$  or  $-\text{CH}_2\text{C}(=\text{O})\text{NH-phenylene-}$ .

48. A compound according to any one of claims 33 to 47 wherein  $L^2$  is a single bond or  $-\text{C}(=\text{O})\text{CH}_2-$ .

49. A compound according to any one of claims 33 to 48 wherein  $L^3$  is a single bond.